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# NOVEL POLYPEPTIDES AND NUCLEIC ACIDS ENCODING SAME

## **RELATED APPLICATIONS**

This application claims priority to USSN 60/171,746, filed December 22, 1999, which is incorporated herein by reference.

### **BACKGROUND OF THE INVENTION**

Mammals are able to discriminate between thousands of odor molecules. This capacity relies on a multigene family encoding 500 - 1000 olfactory receptors (ORX) See Buck et al., (1991) Cell 65, 175-187. These receptors are expressed mainly in the olfactory epithelium and have been found in a number of species including mammals, birds, amphibians, and fish. See Buck et al., supra, (1991) Cell 65, 175-187; Selbie et al., (1992) Mol. Brain Res. 13, 159-163; Rouquier et al., (1998) Nature Genet. 18, 243-50.; Issel-Tarver et al., (1997) Genetics 145, 185-195; Sullivan et al., (1996) Proc. Natl. Acad. Sci. USA 93, 884-888; Nef et al., (1992) Proc. Natl. Acad. Sci USA 89, 8948-8952; Leibovici et al., (1996) Dev. Biol. 175, 118-131; Freitag et al., (1995) Neuron 15, 1383-1392; Ngai et al., (1993) Cell 72, 657-666.

All of these receptors belong to the G protein-coupled receptor (GPCR) superfamily and share features of sequence and structure, such as seven hydrophobic transmembrane domains (7TM).

The sense of smell plays an important role in mammalian social behavior, location of food and detection of predators. However, mammals vary in their olfactory ability. See Moulton (1967) Am. Zool. 7, 421-429; Stoddart (1980) The ecology of vertebrate olfaction (Chapman and Hall, New York).

In primates, the sense of smell is greatly reduced (*i.e.*, microsmatic) with respect to other mammals such as dogs or rodents. *See* Moulton, *supra*; Stoddart, *supra*; Issel-Tarver, L., Rine, J. (1996) *Proc. Natl. Acad. Sci. USA* **93**, 10897-10902.

Various explanations for the differences in olfactory performance have been hypothesized. Differences in the anatomical structures (size, location) devoted to olfaction could partly explain these differences. For example, dogs, which have an olfactory sensitivity up to 100 times greater than humans, have on average ~100 cm<sup>2</sup> of olfactory epithelium while

humans have only 10 cm<sup>2</sup>.

Variations in the size and diversity of the expressed ORX gene family could also account

for these differences. It has recently been demonstrated that the human ORX gene repertoire is distributed in over 25 chromosomal sites. Over 70% of these ORX genes are pseudogenes, *i.e.* the sequences have accumulated deleterious mutations such as in-frame stop codons and/or

indel

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frameshifts. See Rouquier et al., (1998) Nature Genet. 18, 243-50. Thus, the reduction of the sense of smell observed in primates could parallel the reduction of the number of functional ORX genes.

#### SUMMARY OF THE INVENTION

The invention is based, in part, upon the discovery of novel polynucleotide sequences encoding novel polypeptides.

Accordingly, in one aspect, the invention provides an isolated nucleic acid molecule that includes the sequence an ORX nucleic acid molecule or a fragment, homolog, analog or derivative thereof. The nucleic acid can include, e.g., a nucleic acid sequence encoding a polypeptide at least 80% identical to a polypeptide that includes the amino acid sequence of an ORX polypeptide. The nucleic acid can be, e.g., a genomic DNA fragment, or a cDNA molecule.

Also included in the invention is a vector containing one or more of the nucleic acids described herein, and a cell containing the vectors or nucleic acids described herein.

The invention is also directed to host cells transformed with a vector comprising any of the nucleic acid molecules described above.

In another aspect, the invention includes a pharmaceutical composition that includes an ORX nucleic acid and a pharmaceutically acceptable carrier or diluent.

In a further aspect, the invention includes a substantially purified ORX polypeptide, e.g., any of the ORX polypeptides encoded by an ORX nucleic acid, and fragments, homologs, analogs, and derivatives thereof. The invention also includes a pharmaceutical composition that includes an ORX polypeptide and a pharmaceutically acceptable carrier or diluent.

ORX polypeptide. The antibody can be, e.g., a monoclonal or polyclonal antibody, and fragments, homologs, analogs, and derivatives thereof. The invention also includes a pharmaceutical composition including ORX antibody and a pharmaceutically acceptable carrier or diluent. The invention is also directed to isolated antibodies that bind to an epitope on a polypeptide encoded by any of the nucleic acid molecules described above.

The invention also includes kits comprising any of the pharmaceutical compositions described above.

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The invention further provides a method for producing an ORX polypeptide by providing a cell containing an ORX nucleic acid, e.g., a vector that includes an ORX nucleic acid, and culturing the cell under conditions sufficient to express the ORX polypeptide encoded by the nucleic acid. The expressed ORX polypeptide is then recovered from the cell. Preferably, the cell produces little or no endogenous ORX polypeptide. The cell can be, e.g., a prokaryotic cell or eukaryotic cell.

The invention is also directed to methods of identifying an ORX polypeptide or nucleic acid in a sample by contacting the sample with a compound that specifically binds to the polypeptide or nucleic acid, and detecting complex formation, if present.

The invention further provides methods of identifying a compound that modulates the activity of an ORX polypeptide by contacting an ORX polypeptide with a compound and determining whether the ORX polypeptide activity is modified.

The invention is also directed to compounds that modulate ORX polypeptide activity identified by contacting an ORX polypeptide with the compound and determining whether the compound modifies activity of the ORX polypeptide, binds to the ORX polypeptide, or binds to a nucleic acid molecule encoding an ORX polypeptide.

The invention also provides a method for assessing the olfactory acuity of a subject by providing a biological sample comprising nucleic acids from the subject, identifying a plurality of nucleic acid sequences homologous to an olfactory receptor nucleic acid sequence, determining the number of sequences containing open-reading frames, determining the number of sequences containing olfactory receptor pseudogenes, and comparing the number of open-reading frames to the number of pseudogenes to assess the olfactory acuity of the subject. In one embodiment, the invention provides a method of determining the plurality of nucleic acids

using a pair of primers that selectively amplify an olfactory receptor nucleic acid sequence. In a further embodiment, this pair of primers includes OR5B-OR3B (OR5B (TM2), 5'-CCCATGTA(T/C)TT(G/C/T)TT(C/T)CTC(A/G/T)(G/C)(C/T)AA(C/T)(T/C)T(G/A)TC-3' (SEQ ID NO: 432) and 5'-AG(A/G)C(A/T)(A/G)TAIATGAAIGG(A/G)TTCAICAT-3' (SEQ ID NO:433). In a still further embodiment, the ratio of the number of sequences containing open-reading frames to the number of sequences containing olfactory receptor pseudogenes is calculated and compared to a reference ratio for an organism whose olfactory acuity is known.

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Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Other features and advantages of the invention will be apparent from the following detailed description and claims.

#### **BRIEF DESCRIPTION OF THE DRAWINGS**

FIG. 1 is a schematic phylogeny tree of the primate species used in the Examples.

FIG. 2 is a comparison of the deduced protein ORX sequences obtained from the different primate species characterized. The dendogram was established using the PileUp program from the GCG Package. Percent amino acid similarity (ASI) was determined by pairwise sequence comparisons using the Gap program and is indicated along the abscissa of the tree. Sequences obtained from the literature are indicated by an asterisk. For example, human ORX sequences derived from the use of the OR3B/OR5B primers and representing the main ORX families were selected from Rouquier et al., *Nature Genet.* (1998) 18, 243-50 and Rouquier et al. (1998) *Hum. Mol. Genet.* 7, 1337-1345. Dog (CfOLF1 and its human counterpart HsOLF1; CfOLF2) and chicken (COR4) sequences were selected from Issel-Tarver et al. (1997) *Genetics* 145, 185-195 and Leibovici et al., (1996) *Dev. Biol.* 175, 118-131, respectively. ORX families (greater than 40% ASI) are indicated by open circles and

subfamilies (greater than 60% ASI) are indicated by open squares. The main family was arbitrarily named family 1 and subdivided in two groups of subfamilies, 1-I and 1-II, which are indicated by ovals. Group 1-II further comprises subfamilies A and B. Beside each sequence name, black dots indicate sequences derived from the use of the OR3B/OR5B consensus primers, black squares those derived from the OR3.1/7.1 consensus primers, and black rectangles indicate potentially functional genes (uninterrupted ORFs). In the case of HSA 912-93 (black rectangle and double asterisk), the sequence contains only one nonsense point mutation in human, but potentially codes in other primates. *See* Rouquier et al. (1998) *Hum. Mol. Genet.* 7, 1337-1345. In FIG. 2, the following abbreviations are used: human, HSA; chimpanzee, PTR; gorilla, GGO; orangutan, PPY; gibbon, HLA; macaque, MSY; baboon, PPA; marmoset, CJA; squirrel-monkey, SSC and SBO; lemur, EFU and ERU; zebrafish, DRE.

#### DETAILED DESCRIPTION OF THE INVENTION

Included in the invention are the novel nucleic acid sequences and their polypeptides. The sequences are collectively referred to as "ORX nucleic acids" or "ORX polynucleotides" and the corresponding encoded polypeptides are referred to as "ORX polypeptides" or "ORX proteins." Unless indicated otherwise, "ORX" is meant to refer to any of the novel sequences disclosed herein.

The ORX nucleic acids and polypeptides are described in more detail below.

#### OR1

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649 bp DNA PRI 28-FEB-2000 LOCUS AF127814 25 DEFINITION Papio hamadryas olfactory receptor (PPA13) gene, partial cds. ACCESSION AF127814 KEYWORDS SOURCE baboon. ORGANISM Papio hamadryas 30 Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia; Eutheria; Primates; Catarrhini; Cercopithecidae; Cercopithecinae; Papio. REFERENCE 1 (bases 1 to 649) AUTHORS Giorgi, D.G. and Rouquier, S.P. 35 The olfactory gene repertoire in primates and mouse: evidence for reduction of function in primates JOURNAL Unpublished REFERENCE 2 (bases 1 to 649) AUTHORS Giorgi, D.G. and Rouquier, S.P.

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         JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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              Papio.
       REFERENCE 1 (bases 1 to 642)
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        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 642)
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        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille.
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       REFERENCE 1 (bases 1 to 649)
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              reduction of function in primates
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        REFERENCE 1 (bases 1 to 649)
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              reduction of function in primates
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                 The olfactory gene repertoire in primates and mouse: evidence for
               reduction of function in primates
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         JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 649)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
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#### 5 OR6

LOCUS AF127819 649 bp DNA PRI 28-FEB-2000 DEFINITION Papio hamadryas olfactory receptor (PPA42) gene, partial cds. ACCESSION AF127819

10 **KEYWORDS** 

> SOURCE baboon.

ORGANISM Papio hamadryas

Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia; Eutheria; Primates; Catarrhini; Cercopithecidae; Cercopithecinae;

15 Papio.

REFERENCE 1 (bases 1 to 649)

AUTHORS Giorgi, D.G. and Rouquier, S.P.

TITLE The olfactory gene repertoire in primates and mouse: evidence for reduction of function in primates

20 JOURNAL Unpublished

REFERENCE 2 (bases 1 to 649)

AUTHORS Giorgi, D.G. and Rouquier, S.P.

TITLE Direct Submission

JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,

Montpellier Cedex 5 34396, France

**FEATURES** Location/Qualifiers 1..649

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421 agecaegece tteatetgea teetggette etatgetege ateettgegg ceateatgaa

481 ggtcccctct gcaggcggca ggaagaaagc cttctccacc tgcagctccc acctgtctgt

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        REFERENCE 1 (bases 1 to 641)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
                  The olfactory gene repertoire in primates and mouse: evidence for
               reduction of function in primates
15
         JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 641)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
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         JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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       SOURCE
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              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
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              Papio.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
55
        TITLE The olfactory gene repertoire in primates and mouse: evidence for
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reduction of function in primates
         JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 649)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
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         TITLE Direct Submission
         JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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              Papio.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
50
               The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
55
        TITLE Direct Submission
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JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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                                                           28-FEB-2000
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       ACCESSION AF127823
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        ORGANISM Papio hamadryas
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              Eutheria; Primates; Catarrhini; Cercopithecidae; Cercopithecinae;
              Papio.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
45
                The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
50
        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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                                                           28-FEB-2000
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       DEFINITION Pan troglodytes olfactory receptor (PTR12) gene, partial cds.
       ACCESSION AF127824
       KEYWORDS
       SOURCE
                   chimpanzee.
        ORGANISM Pan troglodytes
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              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Catarrhini; Hominidae; Pan.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory gene repertoire in primates and mouse: evidence for
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              reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
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        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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                                                            28-FEB-2000
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                    chimpanzee.
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              Eutheria; Primates; Catarrhini; Hominidae; Pan.
        REFERENCE 1 (bases 1 to 650)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory gene repertoire in primates and mouse: evidence for
         TITLE
              reduction of function in primates
35
        JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 650)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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OR13
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5

LOCUS AF127826 649 bp DNA PRI 28-FEB-2000 10 DEFINITION Pan troglodytes PTR3 pseudogene, partial sequence. ACCESSION AF127826 **KEYWORDS SOURCE** chimpanzee. ORGANISM Pan troglodytes 15 Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Pan. REFERENCE 1 (bases 1 to 649) AUTHORS Giorgi, D.G. and Rouquier, S.P. TITLE The olfactory gene repertoire in primates and mouse: evidence for 20 reduction of function in primates JOURNAL Unpublished REFERENCE 2 (bases 1 to 649) AUTHORS Giorgi, D.G. and Rouquier, S.P. TITLE Direct Submission 25 JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille, Montpellier Cedex 5 34396, France **FEATURES** Location/Qualifiers source 1..649 /organism="Pan troglodytes" 30 /db xref="taxon:9598" <1..>649 gene /gene="PTR3" /pseudo BASE COUNT 146 a 166 c 121 g 216 t 35 ORIGIN 1 ctttgttgat ttctgttatt ccaccacagt tacacccaaa ctgctggaga acttggttgt 61 ggaagacaga accateteet teacaggatg cateatgeaa ttetteetgg egtgtatatg 121 tgcagtggca gaaacattca tgctggcagt gatggcctat gattgatacg tggcagtgtg 181 taaccetttg ctctacacag ttgtcaggtc ccagaaactc tgtgcatcat tagtggcagg 40 241 gecetacaea tggggtataa tetettetet gaeaeteaee tattteetet tgteattate 301 cttetgtggg tetaacatea teaataattt tgtetgtgag gaetetgtea teatetetgt 361 ctcctgctct gacccctaca tcagccaaat gctttgtttt gtcattgcaa tattcaatga 421 ggtgagcagc ttgggagtca tcctcactac ctatattttc atctttattg ctgtcataaa 481 aatgeettet getgttggge accaaaaage tttetetaee tgtgetteee acetgaetge

## **OR14**

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50 **LOCUS** AF127827 651 bp DNA PRI 28-FEB-2000 DEFINITION Pan troglodytes PTR4 pseudogene, partial sequence. ACCESSION AF127827 KEYWORDS **SOURCE** chimpanzee. 55 ORGANISM Pan troglodytes

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        REFERENCE 1 (bases 1 to 651)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
  5
         TITLE The olfactory gene repertoire in primates and mouse: evidence for
               reduction of function in primates
         JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 651)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
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         TITLE Direct Submission
         JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille.
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                   AF127828
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        ACCESSION AF127828
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        ORGANISM Pan troglodytes
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Catarrhini; Hominidae; Pan.
        REFERENCE 1 (bases 1 to 657)
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        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                 The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 657)
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        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
              Montpellier Cedex 5 34396, France
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         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE
                  The olfactory gene repertoire in primates and mouse: evidence for
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         JOURNAL Unpublished
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        REFERENCE 2 (bases 1 to 657)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE Direct Submission
         JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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        REFERENCE 1 (bases 1 to 650)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE The olfactory gene repertoire in primates and mouse: evidence for
               reduction of function in primates
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         JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 650)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE Direct Submission
         JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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        REFERENCE 1 (bases 1 to 663)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE The olfactory gene repertoire in primates and mouse: evidence for
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               reduction of function in primates
         JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 663)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE Direct Submission
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              Eutheria; Primates; Catarrhini; Hominidae; Pan.
        REFERENCE 1 (bases 1 to 677)
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        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 677)
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        AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE Direct Submission
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        REFERENCE 1 (bases 1 to 643)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE The olfactory gene repertoire in primates and mouse; evidence for
               reduction of function in primates
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         JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 643)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE Direct Submission
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               Eutheria; Primates; Catarrhini; Hylobatidae; Hylobates.
        REFERENCE 1 (bases 1 to 648)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE The olfactory gene repertoire in primates and mouse: evidence for
20
               reduction of function in primates
         JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 648)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE Direct Submission
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ORGANISM Hylobates lar

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       REFERENCE 1 (bases 1 to 660)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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        TITLE The olfactory gene repertoire in primates and mouse: evidence for
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        JOURNAL Unpublished
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       ACCESSION AF127836
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              Eutheria; Primates; Catarrhini; Hylobatidae; Hylobates.
       REFERENCE 1 (bases 1 to 649)
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        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                 The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 649)
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        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
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       ACCESSION AF127837
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       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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        TITLE The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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       REFERENCE 1 (bases 1 to 651)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory gene repertoire in primates and mouse: evidence for
35
              reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 651)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
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        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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       REFERENCE 1 (bases 1 to 644)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE The olfactory gene repertoire in primates and mouse: evidence for
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              reduction of function in primates
         JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 644)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
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        SOURCE
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       REFERENCE 1 (bases 1 to 649)
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        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
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        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
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       REFERENCE 1 (bases 1 to 659)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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        TITLE The olfactory gene repertoire in primates and mouse: evidence for
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        REFERENCE 2 (bases 1 to 659)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
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         TITLE Direct Submission
         JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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               Eutheria; Primates; Catarrhini; Hylobatidae; Hylobates.
        REFERENCE 1 (bases 1 to 662)
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         AUTHORS Giorgi, D.G. and Rouquier, S.P.
                 The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 662)
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        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
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              Montpellier Cedex 5 34396, France
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               Eutheria; Primates; Catarrhini; Hominidae; Gorilla.
        REFERENCE 1 (bases 1 to 662)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
                 The olfactory gene repertoire in primates and mouse: evidence for
               reduction of function in primates
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         JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 662)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE Direct Submission
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              Eutheria; Primates; Catarrhini; Hominidae; Gorilla.
       REFERENCE 1 (bases 1 to 650)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory gene repertoire in primates and mouse: evidence for
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              reduction of function in primates
        JOURNAL Unpublished
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         AUTHORS Giorgi, D.G. and Rouquier, S.P.
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        REFERENCE 1 (bases 1 to 649)
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         AUTHORS Giorgi, D.G. and Rouquier, S.P.
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TITLE The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
         JOURNAL Unpublished
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       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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                The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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        TITLE Direct Submission
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        ORGANISM Gorilla gorilla
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              Eutheria; Primates; Catarrhini; Hominidae; Gorilla.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory gene repertoire in primates and mouse: evidence for
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              reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE
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50
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
              Montpellier Cedex 5 34396, France
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              Eutheria; Primates; Catarrhini; Hominidae; Gorilla.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
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        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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              Montpellier Cedex 5 34396, France
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       ACCESSION AF127849
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               Eutheria: Primates: Catarrhini: Hominidae: Gorilla.
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       REFERENCE 1 (bases 1 to 650)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory gene repertoire in primates and mouse: evidence for
               reduction of function in primates
         JOURNAL Unpublished
35
       REFERENCE 2 (bases 1 to 650)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE Direct Submission
         JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
               Montpellier Cedex 5 34396, France
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               Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
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               Eutheria; Primates; Catarrhini; Hominidae; Gorilla.
        REFERENCE 1 (bases 1 to 650)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE The olfactory gene repertoire in primates and mouse: evidence for
               reduction of function in primates
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         JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 650)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE Direct Submission
         JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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        DEFINITION Gorilla gorilla olfactory receptor (GGO71) gene, partial cds.
        ACCESSION AF127851
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                    gorilla.
        SOURCE
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Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;

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Eutheria; Primates; Catarrhini; Hominidae; Gorilla.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory gene repertoire in primates and mouse: evidence for
 5
              reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
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        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
              Montpellier Cedex 5 34396, France
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       DEFINITION Eulemur fulvus olfactory receptor (EFU35) gene, partial cds.
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              Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
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        JOURNAL Unpublished
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REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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              Montpellier Cedex 5 34396, France
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        ORGANISM Eulemur fulvus
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              Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
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       REFERENCE 1 (bases 1 to 645)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                 The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 645)
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        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
              Montpellier Cedex 5 34396, France
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                                                              28-FEB-2000
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        ACCESSION AF127854
        KEYWORDS
        SOURCE
                    Eulemur fulvus.
         ORGANISM Eulemur fulvus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
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              Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
        REFERENCE 1 (bases 1 to 647)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
                 The olfactory gene repertoire in primates and mouse: evidence for
               reduction of function in primates
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         JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 647)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE Direct Submission
         JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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10 DEFINITION Eulemur rubriventer ERU38 pseudogene, partial sequence.

ACCESSION AF127855

**KEYWORDS** 

SOURCE Eulemur rubriventer.

ORGANISM Eulemur rubriventer

Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia; Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.

REFERENCE 1 (bases 1 to 652)

AUTHORS Giorgi, D.G. and Rouquier, S.P.

TITLE The olfactory gene repertoire in primates and mouse: evidence for

reduction of function in primates

JOURNAL Unpublished

REFERENCE 2 (bases 1 to 652)

AUTHORS Giorgi, D.G. and Rouquier, S.P.

TITLE Direct Submission

JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,

Montpellier Cedex 5 34396, France

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  - 421 ctgtatgttt cctgtcacgg ggatcctcta cccctactct aaaattgtct cctccttaat
  - 481 gaggatgtcc tccactgcag gcaagaagaa agcattttcc acctgtgggt ctcacctctc
- 45 541 tgtggtcctc ttgttctatg gaacaggact tggggtctac ctaagttctg ctgtgacccc
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## **OR43**

50 LOCUS AF127856 648 bp DNA PRI 28-FEB-2000 DEFINITION Eulemur rubriventer ERU39 pseudogene, partial sequence. ACCESSION AF127856 KEYWORDS .

SOURCE Eulemur rubriventer.

55 ORGANISM Eulemur rubriventer

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              Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
       REFERENCE 1 (bases 1 to 648)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
 5
        TITLE The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 648)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
10
        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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       ACCESSION AF127857
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        ORGANISM Eulemur rubriventer
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              Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
       REFERENCE 1 (bases 1 to 649)
45
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
50
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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              Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
       REFERENCE 1 (bases 1 to 648)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
40
        TITLE The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 648)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
45
        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
              Montpellier Cedex 5 34396, France
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           481 atetectegg eteaggggaa gtataaagea tttteeacet gtgeatetea eeteteggte
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                                                           28-FEB-2000
       DEFINITION Eulemur fulvus olfactory receptor (EFU57) gene, partial cds.
       ACCESSION AF127859
       KEYWORDS
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       SOURCE
                   Eulemur fulvus.
        ORGANISM Eulemur fulvus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
       REFERENCE 1 (bases 1 to 643)
25
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                 The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 643)
30
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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            541 ctccttattt tattgtacat gcctaggggt gtacttgagt tctgctacac acaactcaca
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                                                              28-FEB-2000
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        ACCESSION AF127860
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               Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
        REFERENCE 1 (bases 1 to 644)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
20
         TITLE The olfactory gene repertoire in primates and mouse: evidence for
               reduction of function in primates
         JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 644)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
25
         TITLE Direct Submission
         JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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       ACCESSION AF127861
       KEYWORDS
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              Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
       REFERENCE 1 (bases 1 to 649)
 5
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
10
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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              Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
55
        TITLE The olfactory gene repertoire in primates and mouse: evidence for
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reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
 5
        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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       ACCESSION AF127863
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              Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
       REFERENCE 1 (bases 1 to 642)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
               The olfactory gene repertoire in primates and mouse: evidence for
50
              reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 642)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
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        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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        ACCESSION AF127864
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         ORGANISM Eulemur fulvus
               Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
               Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
        REFERENCE 1 (bases 1 to 652)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
35
                 The olfactory gene repertoire in primates and mouse: evidence for
               reduction of function in primates
         JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 652)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
40
         TITLE Direct Submission
         JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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       DEFINITION Eulemur fulvus olfactory receptor (EFU87) gene, partial cds.
       ACCESSION AF127865
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        ORGANISM Eulemur fulvus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
       REFERENCE 1 (bases 1 to 649)
20
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
25
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
              Montpellier Cedex 5 34396, France
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               Eutheria; Primates; Catarrhini; Cercopithecidae; Cercopithecinae;
               Macaca.
        REFERENCE 1 (bases 1 to 646)
15
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE The olfactory gene repertoire in primates and mouse: evidence for
               reduction of function in primates
         JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 646)
20
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE Direct Submission
         JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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       ACCESSION AF127867
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       SOURCE
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        ORGANISM Macaca sylvanus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
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55
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REFERENCE 1 (bases 1 to 649)
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                 The olfactory gene repertoire in primates and mouse: evidence for
         TITLE
              reduction of function in primates
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         JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 649)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE Direct Submission
         JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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       ACCESSION AF127868
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50
              Macaca.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
               The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
55
        JOURNAL Unpublished
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REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
 5
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45
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       REFERENCE 1 (bases 1 to 647)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
50
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 647)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
55
              Montpellier Cedex 5 34396, France
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	Eutheria; Primates; Catarrhini; Cercopithecidae; Cercopithecinae;
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	AUTHORS Giorgi, D.G. and Rouquier, S.P.
35	TITLE The olfactory gene repertoire in primates and mouse: evidence for
55	reduction of function in primates
	JOURNAL Unpublished
	REFERENCE 2 (bases 1 to 649)
	AUTHORS Giorgi, D.G. and Rouquier, S.P.
40	TITLE Direct Submission
	JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
	Montpellier Cedex 5 34396, France
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55	Den in relenç i indresorti ditori di distrescoi essie i si sici i sono

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       REFERENCE 1 (bases 1 to 646)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
30
               The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 646)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
35
        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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               Macaca.
        REFERENCE 1 (bases 1 to 649)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
25
                The olfactory gene repertoire in primates and mouse: evidence for
               reduction of function in primates
         JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 649)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
30
         TITLE Direct Submission
         JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
              Montpellier Cedex 5 34396, France
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       REFERENCE 1 (bases 1 to 645)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
20
        TITLE The olfactory gene repertoire in primates and mouse: evidence for
               reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 645)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
25
         TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
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       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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              Eutheria; Primates; Platyrrhini; Callitrichidae; Callithrix.
       REFERENCE 1 (bases 1 to 649)
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        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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TITLE The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
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        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
              Montpellier Cedex 5 34396, France
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              Eutheria; Primates; Platyrrhini; Callitrichidae; Callithrix.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
50
               The olfactory gene repertoire in primates and mouse: evidence for
        TITLE
              reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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TITLE Direct Submission

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JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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              Eutheria; Primates; Platyrrhini; Callitrichidae; Callithrix.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory gene repertoire in primates and mouse: evidence for
45
              reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
50
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
              Montpellier Cedex 5 34396, France
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        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
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        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
35
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        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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         AUTHORS Giorgi, D.G. and Rouquier, S.P.
                  The olfactory gene repertoire in primates and mouse: evidence for
               reduction of function in primates
         JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 649)
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         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE Direct Submission
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       OR68
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                  AF127881
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                                                            28-FEB-2000
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       ACCESSION AF127881
       KEYWORDS
       SOURCE
                   Callithrix jacchus.
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              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Platyrrhini; Callitrichidae; Callithrix.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
20
                 The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
25
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
              Montpellier Cedex 5 34396, France
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          421 gggtggtccc cttgcaggga ttctttactc ttactctaag atagtttcct ccatacgtgc
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ACCESSION AF127883

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       DEFINITION Callithrix jacchus olfactory receptor (CJA80) gene, partial cds.
       ACCESSION AF127882
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       SOURCE
                   Callithrix jacchus.
        ORGANISM Callithrix jacchus
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              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Platyrrhini; Callitrichidae; Callithrix.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory gene repertoire in primates and mouse: evidence for
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              reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
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        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
              Montpellier Cedex 5 34396, France
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          361 gtcctgctct gacacgtcct ccagccagat ggtggtcatg actgagacct tagctgttat
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50
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                               649 bp DNA
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                                                           28-FEB-2000
       DEFINITION Callithrix jacchus olfactory receptor (CJA81) gene, partial cds.
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KEYWORDS
                   Callithrix jacchus.
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        ORGANISM Callithrix jacchus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
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              Eutheria; Primates; Platyrrhini; Callitrichidae; Callithrix.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
10
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
15
              Montpellier Cedex 5 34396, France
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           421 tgttttteet etetetggaa teetataete ttatteteag atttteteet eeateetgag
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45
       OR71
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                               649 bp DNA
                                                    PRI
                                                           28-FEB-2000
       DEFINITION Callithrix jacchus olfactory receptor (CJA82) gene, partial cds.
       ACCESSION AF127884
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       KEYWORDS
       SOURCE
                   Callithrix jacchus.
        ORGANISM Callithrix jacchus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Platyrrhini; Callitrichidae; Callithrix.
55
       REFERENCE 1 (bases 1 to 649)
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AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
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       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
              Montpellier Cedex 5 34396, France
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                               658 bp DNA
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                                                           28-FEB-2000
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       ACCESSION AF127885
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       SOURCE
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        ORGANISM Pongo pygmaeus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Catarrhini; Hominidae; Pongo.
       REFERENCE 1 (bases 1 to 658)
50
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
               The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 658)
55
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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TITLE Direct Submission
         JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
               Montpellier Cedex 5 34396, France
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        DEFINITION Pongo pygmaeus olfactory receptor (PPY11) gene, partial cds.
        ACCESSION AF127886
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        SOURCE
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         ORGANISM Pongo pygmaeus
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               Eutheria; Primates; Catarrhini; Hominidae; Pongo.
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        REFERENCE 1 (bases 1 to 649)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
                 The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
         JOURNAL Unpublished
40
        REFERENCE 2 (bases 1 to 649)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE Direct Submission
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              Montpellier Cedex 5 34396, France
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        KEYWORDS
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        SOURCE
                     orangutan.
         ORGANISM Pongo pygmaeus
               Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
               Eutheria; Primates; Catarrhini; Hominidae; Pongo.
        REFERENCE 1 (bases 1 to 654)
30
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE The olfactory gene repertoire in primates and mouse: evidence for
               reduction of function in primates
         JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 654)
35
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE Direct Submission
         JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
               Montpellier Cedex 5 34396, France
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JOURNAL Unpublished
REFERENCE 2 (bases 1 to 649)
AUTHORS Giorgi, D.G. and Rouquier, S.P.
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TITLE Direct Submission

AF127888

OURCE orangutan.
ORGANISM Pongo pygmaeus

REFERENCE 1 (bases 1 to 649)

AUTHORS Giorgi, D.G. and Rouquier, S.P.

reduction of function in primates

ACCESSION AF127888

**OR75** 

LOCUS

KEYWORDS SOURCE o

5

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JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,

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DEFINITION Pongo pygmaeus olfactory receptor (PPY49) gene, partial cds.

Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;

TITLE The olfactory gene repertoire in primates and mouse: evidence for

649 bp DNA

Eutheria; Primates; Catarrhini; Hominidae; Pongo.

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PRI

28-FEB-2000

Montpellier Cedex 5 34396, France

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ID NO:116).

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**OR76** 

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PRI
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       REFERENCE 1 (bases 1 to 660)
10
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                 The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 660)
15
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory gene repertoire in primates and mouse: evidence for
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        JOURNAL Unpublished
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AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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              Eutheria; Primates; Catarrhini; Hominidae; Pongo.
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                 The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
40
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       REFERENCE 2 (bases 1 to 660)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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               Eutheria; Primates; Catarrhini; Hominidae; Pongo.
        REFERENCE 1 (bases 1 to 633)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
                  The olfactory gene repertoire in primates and mouse: evidence for
25
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        REFERENCE 2 (bases 1 to 633)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
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	REFERENCE 1 (bases 1 to 648)
	AUTHORS Giorgi, D.G. and Rouquier, S.P.
	TITLE The olfactory gene repertoire in primates and mouse: evidence for
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15	JOURNAL Unpublished
	REFERENCE 2 (bases 1 to 648)
	AUTHORS Giorgi, D.G. and Rouquier, S.P.
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20	Montpellier Cedex 5 34396, France
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	Eutheria; Primates; Catarrhini; Hominidae; Pongo.
	REFERENCE 1 (bases 1 to 660)
	AUTHORS Giorgi, D.G. and Rouquier, S.P.
	TITLE The olfactory gene repertoire in primates and mouse: evidence for
55	reduction of function in primates
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JOURNAL Unpublished
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        TITLE Direct Submission
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              Eutheria; Primates; Catarrhini; Hominidae; Pongo.
        REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
40
                 The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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       ACCESSION AF127896
       KEYWORDS
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                   orangutan.
        ORGANISM Pongo pygmaeus
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              Eutheria; Primates; Catarrhini; Hominidae; Pongo.
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        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                 The olfactory gene repertoire in primates and mouse: evidence for
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        JOURNAL Unpublished
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        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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       ACCESSION AF127897
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                   Bolivian squirrel monkey.
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              Eutheria; Primates; Platyrrhini; Cebidae; Cebinae; Saimiri.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
20
                The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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        TITLE Direct Submission
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ACCESSION AF127899

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AF127898
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       ACCESSION AF127898
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       REFERENCE 1 (bases 1 to 646)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory gene repertoire in primates and mouse: evidence for
15
              reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 646)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
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       DEFINITION Saimiri boliviensis olfactory receptor (SBO29) gene, partial cds.
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              Eutheria; Primates; Platyrrhini; Cebidae; Cebinae; Saimiri.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
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        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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       ACCESSION AF127900
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       KEYWORDS
                   Bolivian squirrel monkey.
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        ORGANISM Saimiri boliviensis
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Platyrrhini; Cebidae; Cebinae; Saimiri.
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REFERENCE 1 (bases 1 to 649)

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AUTHORS Giorgi, D.G. and Rouquier, S.P.
               The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
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       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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       SOURCE common squirrel monkey.
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       REFERENCE 1 (bases 1 to 649)
50
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
               The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
55
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Platyrrhini; Cebidae; Cebinae; Saimiri.
       REFERENCE 1 (bases 1 to 646)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
45
                The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 646)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory gene repertoire in primates and mouse: evidence for
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              reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
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        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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       REFERENCE 1 (bases 1 to 646)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
               The olfactory gene repertoire in primates and mouse: evidence for
             reduction of function in primates
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        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 646)
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        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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        REFERENCE 1 (bases 1 to 649)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
                 The olfactory gene repertoire in primates and mouse: evidence for
               reduction of function in primates
         JOURNAL Unpublished
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         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE Direct Submission
         JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
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                 The olfactory gene repertoire in primates and mouse: evidence for
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           421 eggtggteet etegetggga teetgtaete ttaetetaag atagetteet etataegtge
           481 aateteatea getaagggga agtacaagge atttteeace tgtgeatete aceteteagt
           541 tgtctcctta ttttattgta caggcctagg ggtgtacctg agttctgctg caacccacaa
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       OR94
                              649 bp DNA
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                  AF127907
       DEFINITION Saimiri sciureus olfactory receptor (SSC69) gene, partial cds.
       ACCESSION AF127907
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       KEYWORDS
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common squirrel monkey.
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        ORGANISM Saimiri sciureus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Platyrrhini; Cebidae; Cebinae; Saimiri.
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       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory gene repertoire in primates and mouse: evidence for
              reduction of function in primates
        JOURNAL Unpublished
10
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (17-NOV-1999) IGH, CNRS UPR, 141 rue dec la Cardonille,
              Montpellier Cedex 5 34396, France
15
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           181 teaccectg cactacacag teaccattaa ecceagactg tgtggactge tggttetgge
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           481 aateteatea geteagggga agtacaagge gttttecace tgtgeatete acatettaat
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                               487 bp DNA
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       DEFINITION Papio hamadryas olfactory receptor (PPA133) gene, partial cds.
       ACCESSION AF179716
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        ORGANISM Papio hamadryas
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Catarrhini; Cercopithecidae; Cercopithecinae;
              Papio.
55
       REFERENCE 1 (bases 1 to 487)
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AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
 5
       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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           241 agggetgatt ettgteatee eatteetaet eateettggg teetatgeae ggattgtete
           301 etecateete aaggteeett egtetaaggg tatetgeaag gegtteteta ettgtggete
           361 ccacctctct gtggtgtcac tgttctatgg gaccattatt ggtctctact tctgcccatc
           421 agctaatagt tetaetetaa aggagaetgt tatggetatg atgtacaetg tggtgaecee
           481 catgctg (SEQ ID NO:147).
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       OR96
                  AF179717
                               486 bp DNA
                                                   PRI
                                                           31-DEC-2000
       LOCUS
       DEFINITION Papio hamadryas olfactory receptor (PPA134) gene, partial cds.
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       ACCESSION AF179717
       KEYWORDS
       SOURCE
                   baboon.
        ORGANISM Papio hamadryas
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
45
              Eutheria; Primates; Catarrhini; Cercopithecidae; Cercopithecinae;
              Papio.
       REFERENCE 1 (bases 1 to 486)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
50
              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 486)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
55
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
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1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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           181 agtactgagg ctggcaagtg ctgggaagca caggagcgag atctctgtga tgacagccac
           241 tgtagtette attatgatee cettetetet gattgteace tettacatee geateetggg
           301 agecatecta gegatggeet ecacecagag eegeegeaag gtetteteea eetgeteete
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           481 catgct (SEQ ID NO:149).
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                               487 bp DNA
                                                   PRI
                                                           31-DEC-2000
       DEFINITION Papio hamadryas PPA135 pseudogene, partial sequence.
       ACCESSION AF179718
       KEYWORDS
       SOURCE
                   baboon.
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        ORGANISM Papio hamadryas
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Catarrhini; Cercopithecidae; Cercopithecinae;
              Papio.
       REFERENCE 1 (bases 1 to 487)
40
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 487)
45
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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           241 cattetggtg gtcatgatcc cetgettget gatettgtgt tectacacte teattgetge
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       LOCUS
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                                                              31-DEC-2000
       DEFINITION Papio hamadryas PPA136 pseudogene, partial sequence.
       ACCESSION AF179719
       KEYWORDS
       SOURCE
                    baboon.
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         ORGANISM Papio hamadryas
               Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
               Eutheria; Primates; Catarrhini; Cercopithecidae; Cercopithecinae;
               Papio.
       REFERENCE 1 (bases 1 to 482)
25
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
                 The olfactory receptor gene repertoire in primates and mouse:
               Evidence for reduction of function in primates
         JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 482)
30
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE Direct Submission
         JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
               1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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           121 gaccagggtg accttctgtg ggactcaaga gatccactac ctcttctgtg agatgtacgt
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           421 acacctacte catgaaggae teagtageea cagtgatgta tgetgtggtg acacctatga
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**LOCUS** 

AF179720

481 bp DNA

31-DEC-2000

PRI

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DEFINITION Papio hamadryas olfactory receptor (PPA137) gene, partial cds.
       ACCESSION AF179720
       KEYWORDS
       SOURCE
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        ORGANISM Papio hamadryas
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              Eutheria; Primates; Catarrhini; Cercopithecidae; Cercopithecinae;
              Papio.
       REFERENCE 1 (bases 1 to 481)
10
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 481)
15
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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          421 ctccaagage eccetggatg gggeagtgge tgtgttttae aetgttgtea etceatteet
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                                                   PRI
                                                          31-DEC-2000
       DEFINITION Papio hamadryas olfactory receptor (PPA138) gene, partial cds.
       ACCESSION AF179721
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       KEYWORDS
       SOURCE
                   baboon.
        ORGANISM Papio hamadryas
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Catarrhini; Cercopithecidae; Cercopithecinae;
55
              Papio.
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REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
 5
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
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              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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                                                           31-DEC-2000
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       DEFINITION Papio hamadryas olfactory receptor (PPA139) gene, partial cds.
       ACCESSION AF179722
       KEYWORDS
       SOURCE
                   baboon.
        ORGANISM Papio hamadryas
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              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Catarrhini; Cercopithecidae; Cercopithecinae;
              Papio.
       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
50
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
55
        TITLE Direct Submission
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JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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       DEFINITION Papio hamadryas olfactory receptor (PPA140) gene, partial cds.
       ACCESSION AF179723
       KEYWORDS
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       SOURCE
                   baboon.
        ORGANISM Papio hamadryas
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Catarrhini; Cercopithecidae; Cercopithecinae;
              Papio.
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       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
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       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
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              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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                  361 ceacctetet gtggtgteae tgttetatgg gaccattatt ggtetetaet tetgeceate
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               DEFINITION Papio hamadryas olfactory receptor (PPA142) gene, partial cds.
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                     Eutheria; Primates; Catarrhini; Cercopithecidae; Cercopithecinae;
                     Papio.
               REFERENCE 1 (bases 1 to 478)
                AUTHORS Giorgi, D.G. and Rouquier, S.P.
                TITLE The olfactory receptor gene repertoire in primates and mouse:
35
                     Evidence for reduction of function in primates
                JOURNAL Unpublished
               REFERENCE 2 (bases 1 to 478)
                AUTHORS Giorgi, D.G. and Rouquier, S.P.
                TITLE Direct Submission
40
                JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
                     1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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5	121 agcccagtta ccattctgtg gccccaatgt catcgaccac tttatgtgtg atttagtacc
	181 tettetagag etggeetgea eagacactea eacettgggg eetetgatag etgeeaacag
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	301 etecetaagg acteatatet etgaagggeg teacaaaget etgtetagtt gtacetetea 361 tatetttgtt gteatettat tetttgteee ttgtteatae etgtatetaa gaeetetaae
10	421 etectecce aetgacaaag etgtgactgt gttttgcace etatttacae etatgttg (SEQ ID NO:161).
	121 occours as Branch of Parish Sampanos communes com Prof. (C. 2 occours).
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20	ORGANISM Papio hamadryas  Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
20	Eutheria; Primates; Catarrhini; Cercopithecidae; Cercopithecinae;
	Papio.
	REFERENCE 1 (bases 1 to 487)
25	AUTHORS Giorgi, D.G. and Rouquier, S.P.
25	TITLE The olfactory receptor gene repertoire in primates and mouse:  Evidence for reduction of function in primates
	JOURNAL Unpublished
	REFERENCE 2 (bases 1 to 487)
	AUTHORS Giorgi, D.G. and Rouquier, S.P.
30	TITLE Direct Submission
	JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR 1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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50	121 cttacagett gattactgta ggtetaatat tatggaceat tttacetgtg attattttee
	181 cetgetgeaa ettgettgtt cagacacaaa attectagag gtgatgggat tttettgtge
	241 tgtgtttact ctaatgttga ctttggcatt aatatttctg tcctacatat acattatcag
<i>E E</i>	301 aacaatttg agaatteett etgetagtea aaggacaaag geetttteea eatgttette
55	361 ccacatgatt gicateteea tetettatgg cagetgeatt titatgtaca tiaaaccete

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OR105
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               ACCESSION AF179726
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               SOURCE
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                      Papio.
15
               REFERENCE 1 (bases 1 to 487)
                AUTHORS Giorgi, D.G. and Rouquier, S.P.
                TITLE The olfactory receptor gene repertoire in primates and mouse:
                      Evidence for reduction of function in primates
                JOURNAL Unpublished
20
               REFERENCE 2 (bases 1 to 487)
                AUTHORS Giorgi, D.G. and Rouquier, S.P.
                TITLE Direct Submission
                JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
                      1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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50
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               DEFINITION Pan troglodytes olfactory receptor (PTR183) gene, partial cds.
55
               ACCESSION AF179727
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481 catgctg (SEQ ID NO:163).

	KEYWORDS .
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5	Eutheria; Primates; Catarrhini; Hominidae; Pan.
,	REFERENCE 1 (bases 1 to 487)
	AUTHORS Giorgi, D.G. and Rouquier, S.P.
	TITLE The olfactory receptor gene repertoire in primates and mouse:
	Evidence for reduction of function in primates
10	JOURNAL Unpublished
	REFERENCE 2 (bases 1 to 487)
	AUTHORS Giorgi, D.G. and Rouquier, S.P.
	TITLE Direct Submission
1.5	JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
15	1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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	Evidence for reduction of function in primates  JOURNAL Unpublished
	REFERENCE 2 (bases 1 to 487)
	AUTHORS Giorgi, D.G. and Rouquier, S.P.
5	TITLE Direct Submission
	JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
	1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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	121 ggccaggttg tgtttttgtg cagacaatgt gatccccac tttttctgtg atatgtctgc
	181 tctactgaag ctggcctgct ctgacactcg agttaatgaa tgggtgatat ttatcatggg
	241 agggeteatt gttgteatee eatteetaet eateettggg teetatgeaa gaattgtete
30	301 ctccatcctc aaggtccctt cttctaaggg tatctgcaag gccttgtcta cttgtggctc
	361 ccacctgtct gtggtgtcac tgttctatgg gaccgttatt ggtctctact tatgcccatc
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	481 catgctg (SEQ ID NO:169).
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	ORGANISM Pan troglodytes
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45	Eutheria; Primates; Catarrhini; Hominidae; Pan.
43	REFERENCE 1 (bases 1 to 485) AUTHORS Giorgi, D.G. and Rouquier, S.P.
	TITLE The olfactory receptor gene repertoire in primates and mouse:
	Evidence for reduction of function in primates
	JOURNAL Unpublished
50	REFERENCE 2 (bases 1 to 485)
	AUTHORS Giorgi, D.G. and Rouquier, S.P.
	TITLE Direct Submission
	JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
55	1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
33	FEATURES Location/Qualifiers

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                ACCESSION AF179730
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                       Eutheria; Primates; Catarrhini; Hominidae; Pan.
                REFERENCE 1 (bases 1 to 487)
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                 AUTHORS Giorgi, D.G. and Rouquier, S.P.
                 TITLE The olfactory receptor gene repertoire in primates and mouse:
                       Evidence for reduction of function in primates
                 JOURNAL Unpublished
                REFERENCE 2 (bases 1 to 487)
35
                 AUTHORS Giorgi, D.G. and Rouquier, S.P.
                 TITLE Direct Submission
                 JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
                       1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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15	LOCUS AF179731 487 bp DNA PRI 31-DEC-2000 DEFINITION Pan troglodytes olfactory receptor (PTR206) gene, partial cds. ACCESSION AF179731 KEYWORDS SOURCE chimpanzee. ORGANISM Pan troglodytes Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
	Eutheria; Primates; Catarrhini; Hominidae; Pan.
20	REFERENCE 1 (bases 1 to 487)
	AUTHORS Giorgi, D.G. and Rouquier, S.P.  TITLE The olfactory receptor gene repertoire in primates and mouse:  Evidence for reduction of function in primates  JOURNAL Unpublished
25	REFERENCE 2 (bases 1 to 487)
	AUTHORS Giorgi, D.G. and Rouquier, S.P.  TITLE Direct Submission  JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR  1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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	361 teacettgee ttggteatte ttttetatgg ageaateaca ggggtetata tgageceett
55	421 atccaatcac tctactgaaa aagactcagc cgcatcagtc atttttatgg ttgtagcacc 481 tgtgttg (SEQ ID NO:174).
	ייי יוייסיים (שבע אב זיטיזי יוי

5	LOCUS AF179732 487 bp DNA PRI 31-DEC-2000 DEFINITION Pan troglodytes olfactory receptor (PTR207) gene, partial cds. ACCESSION AF179732 KEYWORDS .
10	SOURCE chimpanzee. ORGANISM Pan troglodytes Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Pan. REFERENCE 1 (bases 1 to 487)
15	AUTHORS Giorgi, D.G. and Rouquier, S.P.  TITLE The olfactory receptor gene repertoire in primates and mouse:  Evidence for reduction of function in primates  JOURNAL Unpublished  REFERENCE 2 (bases 1 to 487)
20	AUTHORS Giorgi, D.G. and Rouquier, S.P.  TITLE Direct Submission  JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR  1142, rue de la Cardonille, Montpellier Cedex 5 34396, France  FEATURES Location/Qualifiers
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50	LOCUS AF179733 481 bp DNA PRI 31-DEC-2000 DEFINITION Pan troglodytes olfactory receptor (PTR208) gene, partial cds. ACCESSION AF179733 KEYWORDS .
55	SOURCE chimpanzee. ORGANISM Pan troglodytes

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               REFERENCE 1 (bases 1 to 481)
                AUTHORS Giorgi, D.G. and Rouquier, S.P.
 5
                TITLE The olfactory receptor gene repertoire in primates and mouse:
                      Evidence for reduction of function in primates
                JOURNAL Unpublished
               REFERENCE 2 (bases 1 to 481)
                AUTHORS Giorgi, D.G. and Rouquier, S.P.
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                TITLE Direct Submission
                JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
                      1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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                      Eutheria; Primates; Catarrhini; Hominidae; Pan.
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               REFERENCE 1 (bases 1 to 487)
                AUTHORS Giorgi, D.G. and Rouquier, S.P.
                TITLE The olfactory receptor gene repertoire in primates and mouse:
                      Evidence for reduction of function in primates
                JOURNAL Unpublished
55
               REFERENCE 2 (bases 1 to 487)
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AUTHORS Giorgi, D.G. and Rouquier, S.P.
                TITLE Direct Submission
                JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
                      1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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               REFERENCE 1 (bases 1 to 487)
                AUTHORS Giorgi, D.G. and Rouquier, S.P.
                TITLE The olfactory receptor gene repertoire in primates and mouse:
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                      Evidence for reduction of function in primates
                JOURNAL Unpublished
               REFERENCE 2 (bases 1 to 487)
                AUTHORS Giorgi, D.G. and Rouquier, S.P.
                TITLE Direct Submission
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                JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
                      1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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                  481 cctgcta (SEQ ID NO:182).
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               DEFINITION Pan troglodytes olfactory receptor (PTR211) gene, partial cds.
               ACCESSION AF179736
               KEYWORDS
                           chimpanzee.
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                      Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
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               REFERENCE 1 (bases 1 to 487)
                AUTHORS Giorgi, D.G. and Rouquier, S.P.
35
                TITLE The olfactory receptor gene repertoire in primates and mouse:
                      Evidence for reduction of function in primates
                JOURNAL Unpublished
               REFERENCE 2 (bases 1 to 487)
                AUTHORS Giorgi, D.G. and Rouquier, S.P.
40
                TITLE Direct Submission
                JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
                      1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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	181 ggtcatcaag etegeetgtt etgacaceet catcaacaac atectcatat attttgcaag
10	241 tagcatattt ggtgcaatte etetetetgg aataatttte tettattete aaatagteae
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10	OR116
	LOCUS AF179737 487 bp DNA PRI 31-DEC-2000
	DEFINITION Pan troglodytes olfactory receptor (PTR212) gene, partial cds.
20	ACCESSION AF179737
	KEYWORDS .
	SOURCE chimpanzee.
	ORGANISM Pan troglodytes
25	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Pan.
23	REFERENCE 1 (bases 1 to 487)
	AUTHORS Giorgi, D.G. and Rouquier, S.P.
	TITLE The olfactory receptor gene repertoire in primates and mouse:
••	Evidence for reduction of function in primates
30	JOURNAL Unpublished
	REFERENCE 2 (bases 1 to 487) AUTHORS Giorgi, D.G. and Rouquier, S.P.
	TITLE Direct Submission
	JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
35	1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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55	101 ocigorodag orgreerger cagararen ocioaargag orggreargi reacagragg

5	241 ggtggtggte attaccetge cattcatgtg tatcetggta teatatgget acattgggge 301 caccatectg agggtecett caaccaaagg gatecacaaa gcattgteca catgtggete 361 ccatectet gtggtgtete tetattatgg gteaatattt ggecagtace ttttecegae 421 tgtaagcagt tetattgaca aggatgteat tgtggetete atgtacaegg tggteacace
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15	ORGANISM Hylobates lar Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia; Eutheria; Primates; Catarrhini; Hylobatidae; Hylobates. REFERENCE 1 (bases 1 to 484)
20	AUTHORS Giorgi, D.G. and Rouquier, S.P.  TITLE The olfactory receptor gene repertoire in primates and mouse:  Evidence for reduction of function in primates  JOURNAL Unpublished  REFERENCE 2 (bases 1 to 484)
25	AUTHORS Giorgi, D.G. and Rouquier, S.P. TITLE Direct Submission JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
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45	401 getg (SEQ 1D 140.100).
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50	LOCUS AF179739 487 bp DNA PRI 31-DEC-2000 DEFINITION Hylobates lar olfactory receptor (HLA122) gene, partial cds. ACCESSION AF179739 KEYWORDS . SOURCE common gibbon.
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REFERENCE 1 (bases 1 to 487)
                AUTHORS Giorgi, D.G. and Rouquier, S.P.
                TITLE The olfactory receptor gene repertoire in primates and mouse:
                      Evidence for reduction of function in primates
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               REFERENCE 2 (bases 1 to 487)
                AUTHORS Giorgi, D.G. and Rouquier, S.P.
                TITLE Direct Submission
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                      1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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40
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               SOURCE
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                ORGANISM Hylobates lar
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                      Eutheria; Primates; Catarrhini; Hylobatidae; Hylobates.
               REFERENCE 1 (bases 1 to 486)
                AUTHORS Giorgi, D.G. and Rouquier, S.P.
                       The olfactory receptor gene repertoire in primates and mouse:
50
                      Evidence for reduction of function in primates
                JOURNAL Unpublished
               REFERENCE 2 (bases 1 to 486)
                AUTHORS Giorgi, D.G. and Rouquier, S.P.
                TITLE Direct Submission
55
                JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
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                                                            PRI
                                                                   31-DEC-2000
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               ACCESSION AF179741
               KEYWORDS
               SOURCE
                           common gibbon.
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                ORGANISM Hylobates lar
                      Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
                      Eutheria; Primates; Catarrhini; Hylobatidae; Hylobates.
               REFERENCE 1 (bases 1 to 487)
                AUTHORS Giorgi, D.G. and Rouquier, S.P.
40
                TITLE The olfactory receptor gene repertoire in primates and mouse:
                      Evidence for reduction of function in primates
                JOURNAL Unpublished
               REFERENCE 2 (bases 1 to 487)
                AUTHORS Giorgi, D.G. and Rouquier, S.P.
45
                TITLE Direct Submission
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                      1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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                                                          PRI
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               ACCESSION AF179742
               KEYWORDS
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               ORGANISM Hylobates lar
                     Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
                     Eutheria; Primates; Catarrhini; Hylobatidae; Hylobates.
               REFERENCE 1 (bases 1 to 487)
30
                AUTHORS Giorgi, D.G. and Rouquier, S.P.
                TITLE The olfactory receptor gene repertoire in primates and mouse:
                     Evidence for reduction of function in primates
                JOURNAL Unpublished
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35
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                TITLE Direct Submission
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                     1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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                ACCESSION AF179743
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                 ORGANISM Hylobates lar
                       Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
                       Eutheria; Primates; Catarrhini; Hylobatidae; Hylobates.
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                REFERENCE 1 (bases 1 to 484)
                 AUTHORS Giorgi, D.G. and Rouquier, S.P.
                        The olfactory receptor gene repertoire in primates and mouse:
                       Evidence for reduction of function in primates
                 JOURNAL Unpublished
25
                REFERENCE 2 (bases 1 to 484)
                 AUTHORS Giorgi, D.G. and Rouquier, S.P.
                 TITLE Direct Submission
                 JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
                       1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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5	ACCESSION AF179744
3	KEYWORDS .
	SOURCE common gibbon.
	ORGANISM Hylobates lar
	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
10	Eutheria; Primates; Catarrhini; Hylobatidae; Hylobates.
10	REFERENCE 1 (bases 1 to 487)
	AUTHORS Giorgi, D.G. and Rouquier, S.P.
	TITLE The olfactory receptor gene repertoire in primates and mouse:
	Evidence for reduction of function in primates
15	JOURNAL Unpublished
	REFERENCE 2 (bases 1 to 487)
	AUTHORS Giorgi, D.G. and Rouquier, S.P.
	TITLE Direct Submission
	JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
20	1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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	SOURCE common gibbon.
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55	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
55	Danas joia, iriotazoa, Chorana, Ciamaia, 7 Ottobiaia, iriamminia,

Eutheria; Primates; Catarrhini; Hylobatidae; Hylobates. REFERENCE 1 (bases 1 to 484) AUTHORS Giorgi, D.G. and Rouquier, S.P. TITLE The olfactory receptor gene repertoire in primates and mouse: 5 Evidence for reduction of function in primates JOURNAL Unpublished REFERENCE 2 (bases 1 to 484) AUTHORS Giorgi, D.G. and Rouquier, S.P. TITLE Direct Submission 10 JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR 1142, rue de la Cardonille, Montpellier Cedex 5 34396, France Location/Oualifiers **FEATURES** 1..484 source /organism="Hylobates lar" 15 /db xref="taxon:9580" <1..>484 gene /gene="HLA128" **CDS** <1..>484 /gene="HLA128" 20 /codon start=2 /product="olfactory receptor" /translation="VAICHPLHYTVIMREELCVFLVAVSWILSCASSLSHTLLLTRLS FCAANTIPHVFCDLAALLKLSCSDIFLNELVMFTVGVVVITLPFMCILVSYGYIGATI LRVPSTKGIHKASTCGSHLSVVSLYYGSIFGQYLFPTASSSIDKDVIVAVMYTVITPM 25 L" (SEQ ID NO:202). 87 a 143 c 105 g 149 t BASE COUNT **ORIGIN** 1 tgttgccata tgtcaccctc tccactacac tgtcatcatg agggaagagc tctgtgtctt 61 cttagtggct gtatcttgga ttctgtcttg tgccagctcc ctctctcaca cccttctcct 30 121 gacceggetg tetttetgtg etgegaacae catececeae gtettetgtg acettgetge 181 cctgctcaag ctgtcctgct cagatatett cctcaatgag ctggtcatgt tcacagtagg 241 ggtggtggtc attaccetgc catteatgtg tateetggta teatatgget acattggggc 301 caccatectg agggtccctt caaccaaagg gatccacaaa gcgtccacgt gtggctccca 361 tetttetgtg gtgtetetet attatgggte aatatttgge eagtacettt teeegaeege 35 421 aagcagttcc attgacaagg atgtcattgt ggctgtcatg tacacagtga tcacacccat 481 gttg (SEQ ID NO:201). **OR125** 40 LOCUS AF179746 PRI 31-DEC-2000 484 bp DNA DEFINITION Hylobates lar olfactory receptor (HLA129) gene, partial cds. ACCESSION AF179746 KEYWORDS SOURCE common gibbon. 45 ORGANISM Hylobates lar Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia; Eutheria; Primates; Catarrhini; Hylobatidae; Hylobates. REFERENCE 1 (bases 1 to 484) AUTHORS Giorgi, D.G. and Rouquier, S.P. 50 TITLE The olfactory receptor gene repertoire in primates and mouse: Evidence for reduction of function in primates JOURNAL Unpublished REFERENCE 2 (bases 1 to 484) AUTHORS Giorgi, D.G. and Rouquier, S.P. 55 TITLE Direct Submission

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JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
                      1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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                      Eutheria; Primates; Catarrhini; Hylobatidae; Hylobates.
               REFERENCE 1 (bases 1 to 486)
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                AUTHORS Giorgi, D.G. and Rouquier, S.P.
                        The olfactory receptor gene repertoire in primates and mouse:
                      Evidence for reduction of function in primates
                JOURNAL Unpublished
               REFERENCE 2 (bases 1 to 486)
45
                AUTHORS Giorgi, D.G. and Rouquier, S.P.
                TITLE Direct Submission
                JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
                      1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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	Eutheria; Primates; Catarrhini; Hylobatidae; Hylobates. REFERENCE 1 (bases 1 to 487)
	AUTHORS Giorgi, D.G. and Rouquier, S.P.
25	TITLE The olfactory receptor gene repertoire in primates and mouse:
	Evidence for reduction of function in primates
	JOURNAL Unpublished
	REFERENCE 2 (bases 1 to 487) AUTHORS Giorgi, D.G. and Rouquier, S.P.
30	TITLE Direct Submission
	JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
	1142, rue de la Cardonille, Montpellier Cedex 5 34396, France FEATURES Location/Qualifiers
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                AUTHORS Giorgi, D.G. and Rouquier, S.P.
                TITLE The olfactory receptor gene repertoire in primates and mouse:
                      Evidence for reduction of function in primates
                JOURNAL Unpublished
20
               REFERENCE 2 (bases 1 to 487)
                AUTHORS Giorgi, D.G. and Rouquier, S.P.
                TITLE Direct Submission
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                      1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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                                                                  31-DEC-2000
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5	Eutheria; Primates; Catarrhini; Hominidae; Gorilla.
	REFERENCE 1 (bases 1 to 487)
	AUTHORS Giorgi, D.G. and Rouquier, S.P.
	TITLE The olfactory receptor gene repertoire in primates and mouse:
	Evidence for reduction of function in primates
10	JOURNAL Unpublished
	REFERENCE 2 (bases 1 to 487)
	AUTHORS Giorgi, D.G. and Rouquier, S.P.
•	TITLE Direct Submission
	JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
15	1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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Evidence for reduction of function in primates
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                 AUTHORS Giorgi, D.G. and Rouquier, S.P.
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                 JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
                       1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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                 AUTHORS Giorgi, D.G. and Rouquier, S.P.
                         The olfactory receptor gene repertoire in primates and mouse:
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                      Evidence for reduction of function in primates
                 JOURNAL Unpublished
                REFERENCE 2 (bases 1 to 487)
                 AUTHORS Giorgi, D.G. and Rouquier, S.P.
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                       1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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                ACCESSION AF179753
                KEYWORDS
                            gorilla.
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                       Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
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                REFERENCE 1 (bases 1 to 488)
                 AUTHORS Giorgi, D.G. and Rouquier, S.P.
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                         The olfactory receptor gene repertoire in primates and mouse:
                       Evidence for reduction of function in primates
                 JOURNAL Unpublished
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35
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                       1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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## OR133

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15	TITLE The olfactory receptor gene repertoire in primates and mouse:  Evidence for reduction of function in primates  JOURNAL Unpublished  REFERENCE 2 (bases 1 to 458)  AUTHORS Giorgi, D.G. and Rouquier, S.P.  TITLE Direct Submission
20	JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR 1142, rue de la Cardonille, Montpellier Cedex 5 34396, France FEATURES Location/Qualifiers source 1458
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	SOURCE gorilla.  ORGANISM Gorilla gorilla  Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;  Eutheria; Primates; Catarrhini; Hominidae; Gorilla.
50	REFERENCE 1 (bases 1 to 477)  AUTHORS Giorgi, D.G. and Rouquier, S.P.  TITLE The olfactory receptor gene repertoire in primates and mouse:  Evidence for reduction of function in primates
55	JOURNAL Unpublished REFERENCE 2 (bases 1 to 477)

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AUTHORS Giorgi, D.G. and Rouquier, S.P.
                TITLE Direct Submission
                JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
                      1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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                ACCESSION AF179756
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                AUTHORS Giorgi, D.G. and Rouquier, S.P.
                TITLE The olfactory receptor gene repertoire in primates and mouse:
                      Evidence for reduction of function in primates
                JOURNAL Unpublished
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                AUTHORS Giorgi, D.G. and Rouquier, S.P.
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                 TITLE The olfactory receptor gene repertoire in primates and mouse:
                      Evidence for reduction of function in primates
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               REFERENCE 1 (bases 1 to 487)
15
                AUTHORS Giorgi, D.G. and Rouquier, S.P.
                TITLE The olfactory receptor gene repertoire in primates and mouse:
                      Evidence for reduction of function in primates
                JOURNAL Unpublished
               REFERENCE 2 (bases 1 to 487)
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                AUTHORS Giorgi, D.G. and Rouquier, S.P.
                TITLE Direct Submission
                JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
                      1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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               REFERENCE 1 (bases 1 to 487)
                AUTHORS Giorgi, D.G. and Rouquier, S.P.
                TITLE The olfactory receptor gene repertoire in primates and mouse:
                      Evidence for reduction of function in primates
                JOURNAL Unpublished
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               REFERENCE 2 (bases 1 to 487)
                AUTHORS Giorgi, D.G. and Rouquier, S.P.
                TITLE Direct Submission
                JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
                      1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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                      Eutheria; Primates; Catarrhini; Hominidae; Homo.
               REFERENCE 1 (bases 1 to 487)
                AUTHORS Giorgi, D.G. and Rouquier, S.P.
                TITLE The olfactory receptor gene repertoire in primates and mouse:
                      Evidence for reduction of function in primates
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                JOURNAL Unpublished
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REFERENCE 2 (bases 1 to 487)
                AUTHORS Giorgi, D.G. and Rouquier, S.P.
                TITLE Direct Submission
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       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory receptor gene repertoire in primates and mouse:
45
              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
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        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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        REFERENCE 1 (bases 1 to 486)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
35
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 486)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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              Eutheria; Primates; Catarrhini; Hominidae; Homo.
       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
20
              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
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        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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        TITLE The olfactory receptor gene repertoire in primates and mouse:
               Evidence for reduction of function in primates
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        REFERENCE 2 (bases 1 to 485)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
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        REFERENCE 1 (bases 1 to 486)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
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                 The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 487)
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        TITLE Direct Submission
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        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
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        JOURNAL Unpublished
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           241 ggtggtggtc attaccctgc cattcatgtg tatcctggta tcatatggct acattggggc
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ACCESSION AF179768

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       REFERENCE 1 (bases 1 to 478)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
10
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 478)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
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              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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          241 tggtctgctg tctcttgtct gcttcttggt cttactattc tcttatgcta tcatcctgat
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       ACCESSION AF179769
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              Eutheria; Primates; Catarrhini; Hominidae; Homo.
       REFERENCE 1 (bases 1 to 488)
45
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 488)
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        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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          421 cttctgagac atctatacaa caggggaaaa ttgtagctgt tttttatatc tttgtgagtc
          481 cgatgtta (SEQ ID NO:239).
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       LOCUS
                  AF179770
                               487 bp DNA
                                                    PRI
                                                           31-DEC-2000
       DEFINITION Homo sapiens olfactory receptor (HSA8) gene, partial cds.
       ACCESSION AF179770
       KEYWORDS
       SOURCE
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        ORGANISM Homo sapiens
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Catarrhini; Hominidae; Homo.
       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
30
                 The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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           361 teacatgatt gteattteea tttettatgg aagetgtata tteatgtatg etaateeate
           421 tgcaaaagaa aaggcatcat tgacaaaagg aatagctatt ctcaatacat ctgttgcccc
           481 catgctg (SEQ ID NO:240).
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       LOCUS
                   AF179771
                                485 bp DNA
                                                    PRI
                                                            31-DEC-2000
       DEFINITION Eulemur fulvus olfactory receptor (EFU145) gene, partial cds.
       ACCESSION AF179771
       KEYWORDS
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       SOURCE
                    Eulemur fulvus.
        ORGANISM Eulemur fulvus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
       REFERENCE 1 (bases 1 to 485)
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        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 485)
25
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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           181 teteetgaag etegeetget eggataeeeg cataaaegag etgatgatea tegeeatggg
           241 cttggcette cteaeggtte eceteaeget gategtette teetaegtee geateteetg
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           301 ggetgtgett ggeatetegt eteetggagg gegatgeaaa geetteteea eetgtggtte
           361 teateteacg gtggttetge tettetatgg gtetettatg ggtgtgtatt tgetteetee
           421 gtcatcttac tctacagaga gggaaagcag ggctgccatt ctctacatgg tgatcattcc
           481 catgt (SEQ ID NO:242).
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121 cctccagctg gattactgtg cttccaacgt cattgatcac tttgcatgtg actattttcc

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**OR151** 

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                   AF179772
                               485 bp DNA
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                                                            31-DEC-2000
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       ACCESSION AF179772
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       KEYWORDS
       SOURCE
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        ORGANISM Eulemur fulvus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
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       REFERENCE 1 (bases 1 to 485)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
15
       REFERENCE 2 (bases 1 to 485)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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           301 gattgtcagg atcccctctg tccaggagag gaaaaaggct ttctccacct gttcctccca
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           361 tgtcatcgtg gttaccatgt gctatggaaa gctgttttt tatgtatgtc aagccctccc
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           481 tcttg (SEQ ID NO:244).
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                  AF179773
                               487 bp DNA
                                                    PRI
                                                            31-DEC-2000
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       ACCESSION AF179773
       KEYWORDS
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       SOURCE
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        ORGANISM Eulemur fulvus
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              Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
       REFERENCE 1 (bases 1 to 487)
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        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 487)
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        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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                                                           31-DEC-2000
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                               487 bp DNA
                                                   PRI
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       ACCESSION AF179774
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        ORGANISM Eulemur fulvus
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              Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
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       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
45
       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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                  ML" (SEQ ID NO:248).
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          481 catgctg (SEQ ID NO:247).
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                              487 bp DNA
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                                                         31-DEC-2000
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       DEFINITION Eulemur fulvus olfactory receptor (EFU149) gene, partial cds.
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       ACCESSION AF179775
       KEYWORDS
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        ORGANISM Eulemur fulvus
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             Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
             Evidence for reduction of function in primates
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        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
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              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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BASE COUNT

109 a 113 c 91 g 174 t

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           181 cctgctgcag ctttcctgtt cagatacaaa attcctggag ataatggggt tttcctgtgc
           241 tgtgtttact ctaatgttca ctttggcatt aatatttctg tcctacatgc acatcgtgag
           301 aacgattttg agaatteett etaetagtea gaggacaaag geetttteta eatgttette
           361 ccacatgatt gtcatctcca tctcttatgg cagctgcatt tttatgtaca ttaagccctc
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        DEFINITION Eulemur fulvus EFU150 pseudogene, partial sequence.
        ACCESSION AF179776
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               Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
               Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
        REFERENCE 1 (bases 1 to 484)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE The olfactory receptor gene repertoire in primates and mouse:
25
               Evidence for reduction of function in primates
         JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 484)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE Direct Submission
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         JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
               1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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           481 gttc (SEQ ID NO:251).
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                                                              31-DEC-2000
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**ORIGIN** 

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ACCESSION AF179777

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KEYWORDS
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              Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
10
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
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              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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           121 cagtggcctg teettetgtg gegeeegtge cateaaceae ttettetgtg acattgeace
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           181 ctggattgcc ctggcctgca ccagcacaca ggcaatagag ctcgtggcct ttgtgattgc
           241 ttttgtggtc atcctgagtt catgcctcat caccctggtc tcctacgtgt acattatcag
           301 caccatecte aggateceat etgecagegg eeggageaaa geetteteta egtgeteete
           361 teaceteace gtggtgetea tetggtatgg gteeacgatt tttetteatg teegeacete
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                  AF179778
                               487 bp DNA
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       DEFINITION Eulemur fulvus olfactory receptor (EFU153) gene, partial cds.
       ACCESSION AF179778
       KEYWORDS
       SOURCE
                   Eulemur fulvus.
        ORGANISM Eulemur fulvus
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              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
```

Evidence for reduction of function in primates

55

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JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
 5
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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                   ML" (SEQ ID NO:255).
                        109 a 113 c 91 g 174 t
       BASE COUNT
       ORIGIN
            1 tgttgctatc tgtaagcccc tgcattacag ggtcatcatg aatcgaagag tctgcacact
           61 getegtettt geetettgge tggttteatt ettaategta tteccageae teatgttget
25
           121 cttaaagctt gattactgtg gatttaatat tattgaccat tttacctgtg attattttcc
           181 cctgctgcag ctttcctgtt cagatacaaa attcctggag ataatggggt tttcctgtgc
           241 tgtgtttact ctaatgttca ctttggcatt aatatttctg tcctacatgc acatcgtgag
           301 gacgattttg agaatteett etaetagtea gaggacaaag geetttteta eatgttette
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           421 agcaaaagat agagtatett tgagcaagge agtggetgtg etaateacet eagtagetee
           481 catgete (SEQ ID NO:254).
       OR158
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                                                    PRI
                                                           31-DEC-2000
       LOCUS
                               488 bp DNA
                  AF179779
       DEFINITION Eulemur fulvus olfactory receptor (EFU154) gene, partial cds.
       ACCESSION AF179779
       KEYWORDS
                  Eulemur fulvus.
       SOURCE
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        ORGANISM Eulemur fulvus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
       REFERENCE 1 (bases 1 to 488)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
45
                 The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 488)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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                         92 a 163 c 95 g 138 t
       BASE COUNT
       ORIGIN
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           61 cetggcatet ggetgetggt teetgggate agtagatgge tteatgetea etecaateae
           121 catgacette cectaetgea ggteeeggga gatteaceat teettetgeg aagteeetge
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           241 tgtcctcatg ctcctcattc ctgtgacagt catttcaage tcctattcat tcattctcct
           301 caccatceae aggatggget cageagaggg eeggaagaag geetttgeea eetgtteete
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           361 ccacatgace gtggttatee tettetatgg ggeegecate tacacetaca tgeteeceag
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           481 tgtgctaa (SEQ ID NO:256).
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                               488 bp DNA
       LOCUS
                  AF179780
                                                    PRI
                                                           31-DEC-2000
       DEFINITION Eulemur fulvus EFU155 pseudogene, partial sequence.
       ACCESSION AF179780
       KEYWORDS
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       SOURCE
                   Eulemur fulvus.
        ORGANISM Eulemur fulvus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
       REFERENCE 1 (bases 1 to 488)
35
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 488)
40
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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           121 tettaaaget tgattaetgt ggatttaata ttattgacea ttttaeetgt gattatttte
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241 ctgtgtttac tctaatgttc actttggcat taatatttct gtcctacatg cacatcgtga
301 gaacgatttt gagaatteet tetaetagte agaggacaaa ggeettttet acatgttett
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361 cccacatgat tgtcatctcc atctcttatg gcagctgcat ttttatgtac attaagccct

421 cagcaaagga tagagtatet ttgagcaagg cagtggetgt getaateace teagtagete

481 ccatgcac (SEQ ID NO:258).

## **OR160**

5

486 bp DNA 10 PRI 31-DEC-2000 LOCUS AF179781 DEFINITION Eulemur fulvus EFU156 pseudogene, partial sequence. ACCESSION AF179781 **KEYWORDS** 

SOURCE Eulemur fulvus.

15 ORGANISM Eulemur fulvus

> Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia; Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.

REFERENCE 1 (bases 1 to 486)

AUTHORS Giorgi, D.G. and Rouquier, S.P.

20 TITLE The olfactory receptor gene repertoire in primates and mouse: Evidence for reduction of function in primates

JOURNAL Unpublished

REFERENCE 2 (bases 1 to 486)

AUTHORS Giorgi, D.G. and Rouquier, S.P.

25 TITLE Direct Submission

> JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR 1142, rue de la Cardonille, Montpellier Cedex 5 34396, France

Location/Qualifiers **FEATURES** 

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- 61 teteateate tgttgttggg tggetggttt atgeataata ateceteeae ttageetggg
- 121 tttaaatcta aaattctgtg actctaacat gattgatcat tttggttgcg atgcatttcc
- 40 181 cctggtgaaa atctcatgct cagacacatg gttcatggaa cagacggtta tcatctgtgc
  - 241 tgtgctgacc ctgaatatga ctctaacttg tgtagttctg tcatacgctt acatcatcaa
  - 301 gacaattttt agatteett etgteeagea aaggaaaaag geetttteea eetgttette
  - 361 ccacatgatt gtggtttcca tcacctatgg cacgtgcatt ttcatctaca tgaatcctac
  - 421 agcaaaggaa gaagtgaccg ttaataaagt agtttctttg ctcatttctt ctattttgct
- 45 481 acattg (SEQ ID NO:259).

## **OR161**

PRI 31-DEC-2000 LOCUS AF179782 486 bp DNA

50 DEFINITION Eulemur rubriventer ERU157 pseudogene, partial sequence.

ACCESSION AF179782

**KEYWORDS** 

Eulemur rubriventer. SOURCE

ORGANISM Eulemur rubriventer

55 Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;

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Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
       REFERENCE 1 (bases 1 to 486)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
 5
              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 486)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
10
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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           181 teteetgaag etegeetget eggataeeeg cataaatgag etgatgatea tegeeatggg
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           241 cttgacgttc ctcactattc ccctcacact gategtettc tectacgtcc gcateteetg
           301 ggctgtgctt ggcatctcgt ctcctggcgg gcgatgcaag gccttctcca cctgtggttc
           361 teateteacg gtggttetge tettetatgg gtetettatg ggtgtgtatt tgetteetee
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           481 atgtta (SEQ ID NO:260).
30
       OR162
                               484 bp DNA
                                                     PRI
       LOCUS
                   AF179783
                                                            31-DEC-2000
       DEFINITION Eulemur rubriventer ERU159 pseudogene, partial sequence.
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       ACCESSION AF179783
       KEYWORDS
       SOURCE
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        ORGANISM Eulemur rubriventer
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
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              Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
       REFERENCE 1 (bases 1 to 484)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                 The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
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        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 484)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
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              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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           121 aatgatattg cetttetgtg geaataatgt cattgateat attacetgtg agateetgge
           181 tettaaacte atatgeteag atattteeat gaatgtgett ateatggeag tggeaagtat
           241 tgttatattg gtgatteete tgetgtteat ttttatetee tatgtattea teetetette
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           301 catectgaga attaattett etgaggggag aaagaaagee tttgeaacet gtteageeea
           361 cetgactgtg gtcatettat tetatggtte agetetttt atgtacatga ageetaagte
           421 aaagtacaca aaagtatetg atgaaateat tgeaetgtet taeggagtag taaccecaat
           481 gttg (SEQ ID NO:261).
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       OR163
                                                    PRI
                                                            31-DEC-2000
       LOCUS
                   AF179784
                                487 bp DNA
       DEFINITION Eulemur rubriventer olfactory receptor (ERU160) gene, partial cds.
       ACCESSION AF179784
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       KEYWORDS
       SOURCE
                   Eulemur rubriventer.
        ORGANISM Eulemur rubriventer
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
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       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
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       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
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                    ML" (SEQ ID NO:263).
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           61 attggtgget atateetgge teetgtettg tgeeagetee eteteceaea ecetteteet
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           181 tetgeteaag etgteetget eagacatett eeteaatgag etggteatgt ttacagtagg
55
           241 ggtggtggtc attaccttgc cattettatg tatcctggta tettacggct acattggggc
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301 caccatectg agggteeett caaccaaagg gatetgeaaa geattateea egtgtgggte
           361 ccatctetet gtggtgtete tgtactaegg ggeaatattt gggeagtaee tttteeeage
           421 attaagcaat teeattgaca aggacateat tgtggetatg atgtacaegg tggteacaec
           481 catgttg (SEQ ID NO:262).
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       OR164
       LOCUS
                  AF179785
                               475 bp DNA
                                                    PRI
                                                           31-DEC-2000
       DEFINITION Eulemur rubriventer olfactory receptor (ERU161) gene, partial cds.
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       ACCESSION AF179785
       KEYWORDS
       SOURCE
                   Eulemur rubriventer.
        ORGANISM Eulemur rubriventer
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
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              Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
       REFERENCE 1 (bases 1 to 475)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
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        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 475)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
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              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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       NO:265).
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           181 attattcaag cttgcctgca ccgacacctt tgtagagggg ctgactgtgt tggccaatag
           241 tggcttaatt cccgtgtgct ccctgtttat cctggtgtcc tcctatatca ttattctggt
           301 geacttgagg aaacattetg cagaggggag geacaaagee etetetacet gtgeetetea
           361 catcacggtg gtcattttgt tttttggacc tgccatcttc ctctacatgc gaccttcctc
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50
       OR165
                  AF179786
                               487 bp DNA
                                                    PRI
                                                            31-DEC-2000
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DEFINITION Eulemur rubriventer olfactory receptor (ERU162) gene, partial cds.

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ACCESSION AF179786

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KEYWORDS
                  Eulemur rubriventer.
       SOURCE
        ORGANISM Eulemur rubriventer
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
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              Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
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        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
15
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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                  TL" (SEQ ID NO:267).
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       BASE COUNT
                        91 a 158 c 98 g 140 t
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           61 tttcattatc tgttcataca ctggaggctt tgttaatgca ataatattaa ccagcaacac
          121 atteacgttg gatttttgtg gtgacaatgt catcgacgac tttttctgtg atgtcccacc
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          241 ggcctccaac gtcatctccc eggccatgct catectegcc tectacgtct teatcatege
          301 ageagtettg agggteeget eeageegggg eegeeteaag geetteteea egtgeteete
          361 ccacctgate tetgttacet tatactacgg etecattete tacatetact etegeceaag
          421 ttccagctat tccctcgaga gggacaaaat ggtctctacc ttttacaccg tgctgttccc
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          481 cacgctc (SEQ ID NO:266).
       OR166
                  AF179787
                              478 bp DNA
                                                  PRI
                                                         31-DEC-2000
       LOCUS
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       DEFINITION Eulemur rubriventer olfactory receptor (ERU163) gene, partial cds.
       ACCESSION AF179787
       KEYWORDS
       SOURCE
                  Eulemur rubriventer.
        ORGANISM Eulemur rubriventer
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              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
       REFERENCE 1 (bases 1 to 478)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
```

Evidence for reduction of function in primates

55

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JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 478)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
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        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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           241 tggtetgeta tetettgtet gettettggt ettgatatte tettatgeea ceateetgae
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          361 cctaatggtg gtcagcctga tctttgtgcc atgtgtattc atctacttga ggcctttctg
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       LOCUS
                  AF179788
                               487 bp DNA
                                                   PRI
                                                           31-DEC-2000
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        ORGANISM Eulemur rubriventer
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              Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory receptor gene repertoire in primates and mouse:
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              Evidence for reduction of function in primates
        JOURNAL Unpublished
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        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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           121 tetgeagttg gaettetgtg cetecaatat aattgateat titatetgtg attettetee
           181 aattetgeag etttettgta caaacactea etttetagaa eteatggeat tttgtttage
           241 cgtggtgaca ctcatggtca ccttgacctt agttattctc tcctatacaa atattatccg
           301 gacaatteta agaatteett etatgagtea aaggaaaaaa geetttteea ettgtteete
           361 ccatataata gttgtttccc tctcttatgg tagttgtatc ttcatgtaca taaagccttc
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           421 tacaagggaa agggtgactt taagcaaagg agtagctgtg gttaatactt cagtggctcc
           481 tcttttg (SEQ ID NO:270).
       OR168
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       LOCUS
                  AF179789
                               483 bp DNA
                                                    PRI
                                                            31-DEC-2000
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       ACCESSION AF179789
       KEYWORDS
       SOURCE
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              Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
       REFERENCE 1 (bases 1 to 483)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 483)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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   421 caggeaaagg ggttgateta aacaaaggag tgtettaate aatacaatta ttgeeceet
   481 ctt (SEQ ID NO:272).
OR169
LOCUS
           AF179790
                       486 bp DNA
                                            PRI
                                                    31-DEC-2000
DEFINITION Eulemur rubriventer olfactory receptor (ERU167) gene, partial cds.
ACCESSION AF179790
KEYWORDS
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            Eulemur rubriventer.
 ORGANISM Eulemur rubriventer
      Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
      Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
REFERENCE 1 (bases 1 to 486)
 AUTHORS Giorgi, D.G. and Rouquier, S.P.
 TITLE The olfactory receptor gene repertoire in primates and mouse:
      Evidence for reduction of function in primates
 JOURNAL Unpublished
REFERENCE 2 (bases 1 to 486)
 AUTHORS Giorgi, D.G. and Rouquier, S.P.
 TITLE Direct Submission
 JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
      1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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241 tggtggcact getcagcace ttggtgctga tcaccetgte ctacatecag atcateagga

## **OR170**

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40

45

50

55 LOCUS AF179791 487 bp DNA PRI 31-DEC-2000

481 ctgttg (SEQ ID NO:273).

421 agtttctgac tcttcaagga ggactgcggt ggcttcagtg atgtacactg tggtcactcc

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DEFINITION Eulemur rubriventer olfactory receptor (ERU168) gene, partial cds.
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       KEYWORDS
                   Eulemur rubriventer.
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        ORGANISM Eulemur rubriventer
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Strepsirhini; Lemuridae; Eulemur.
       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
10
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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           181 ggtcgtcaag ctcgcgtgct ccgataccct cgtcaacaac cttctgatct attttgcagc
           241 ttgcaccttg ggtggcattc ctctgtctgg catcattttt tcttacactc aaatagccac
           301 ctccattttg aaaatgccgt catcgggcag aaagtataaa gccttttccg cctgtgggtc
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          481 cgtgttg (SEQ ID NO:275).
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       LOCUS
                  AF179792
                               486 bp DNA
                                                   PRI
                                                           31-DEC-2000
       DEFINITION Macaca sylvanus olfactory receptor (MSY172) gene, partial cds.
       ACCESSION AF179792
       KEYWORDS
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       SOURCE
                   Barbary ape.
        ORGANISM Macaca sylvanus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Catarrhini; Cercopithecidae; Cercopithecinae;
              Macaca.
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       REFERENCE 1 (bases 1 to 486)
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AUTHORS Giorgi, D.G. and Rouquier, S.P.
               The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
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        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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          241 atcctgctgc tgcctgtgcc cctggcattc atttgcctgt cctacttgct catcctggcc
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          481 atgttg (SEQ ID NO:277).
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                              489 bp DNA
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       DEFINITION Macaca sylvanus MSY173 pseudogene, partial sequence.
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       KEYWORDS
       SOURCE
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        ORGANISM Macaca sylvanus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
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              Eutheria; Primates; Catarrhini; Cercopithecidae; Cercopithecinae;
       REFERENCE 1 (bases 1 to 489)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
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              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 489)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
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JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR

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           481 atgtagatt (SEQ ID NO:279).
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       REFERENCE 1 (bases 1 to 481)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory receptor gene repertoire in primates and mouse:
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              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 481)
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        TITLE Direct Submission
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        REFERENCE 1 (bases 1 to 402)
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         AUTHORS Giorgi, D.G. and Rouquier, S.P.
                 The olfactory receptor gene repertoire in primates and mouse:
               Evidence for reduction of function in primates
         JOURNAL Unpublished
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         AUTHORS Giorgi, D.G. and Rouquier, S.P.
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        ACCESSION AF179796
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92 a 126 c 97 g 166 t

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       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory receptor gene repertoire in primates and mouse:
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              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
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          481 tatgttg (SEQ ID NO:283).
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                  AF179797
                               487 bp DNA
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                                                           31-DEC-2000
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       ACCESSION AF179797
       KEYWORDS
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              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Catarrhini; Cercopithecidae; Cercopithecinae;
              Macaca.
       REFERENCE 1 (bases 1 to 487)
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        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 487)
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        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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           181 cetgeteaag ttgteetget eagacacete ceteaateag ttageaatet ttacageagg
           241 attgacagee attatgette catteetgtg tateetggtt tettatggte acaetgeagt
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           301 caccatecte cagattecet etaetaatgg catatgeaaa geettgteea ettgtggate
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           421 atccagcaac actaatgaca agaacataat tgcttcagtg atatacacag tagtcactcc
          481 catgttg (SEQ ID NO:285).
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       OR177
       LOCUS
                  AF179798
                              487 bp DNA
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       DEFINITION Macaca sylvanus olfactory receptor (MSY178) gene, partial cds.
       ACCESSION AF179798
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       KEYWORDS
       SOURCE
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        ORGANISM Macaca sylvanus
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              Eutheria; Primates; Catarrhini; Cercopithecidae; Cercopithecinae;
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              Macaca.
       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
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        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
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                   ML" (SEQ ID NO:288).
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           181 tetgetgaag etggeetget etgacaetea agttaatgaa ttggegatat ttateaeggg
          241 agggetgatt ettgtcatce cattectact catcettggg teetatgeac ggattgtete
          301 etceateete aaggteeett egtetaaggg tatetgeaag geetteteta ettgtggete
          361 ccacctctct gtggtgtcac tgttctatgg gaccgttatt ggtctctact tctgcccatc
          421 agctaatagt tetaetetaa aggagaetgt eatggetatg atgtaeactg tggtgaecee
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          481 catgctg (SEQ ID NO:287).
       OR178
       LOCUS
                  AF179799
                               484 bp DNA
                                                   PRI
                                                           31-DEC-2000
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       DEFINITION Macaca sylvanus olfactory receptor (MSY179) gene, partial cds.
       ACCESSION AF179799
       KEYWORDS
       SOURCE
                   Barbary ape.
        ORGANISM Macaca sylvanus
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              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Catarrhini; Cercopithecidae; Cercopithecinae;
              Macaca.
       REFERENCE 1 (bases 1 to 484)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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                The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 484)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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           181 attgctgagg ctggcatgtt ccgacactca gattaatcac acagtgctga ttgccacagg
           241 etgetttate tteeteatte cetttggatt eatgateatt teetatgtgt tgattgteag
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           481 gatg (SEQ ID NO:289).
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                               487 bp DNA
                                                     PRI
                                                            31-DEC-2000
       LOCUS
                  AF179800
       DEFINITION Macaca sylvanus MSY180 pseudogene, partial sequence.
       ACCESSION AF179800
       KEYWORDS
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       SOURCE
                   Barbary ape.
        ORGANISM Macaca sylvanus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Catarrhini; Cercopithecidae; Cercopithecinae;
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       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
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       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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421 tgtaagcagt tetattgaca aggatgttac tgtggctete atgtacateg tggtcacace
          481 cgtgttg (SEQ ID NO:291).
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                               487 bp DNA
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                  AF179801
       DEFINITION Macaca sylvanus MSY181 pseudogene, partial sequence.
       ACCESSION AF179801
       KEYWORDS
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                   Barbary ape.
       SOURCE
        ORGANISM Macaca sylvanus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Catarrhini; Cercopithecidae; Cercopithecinae;
              Macaca.
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       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
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       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
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           241 ggtggtggtc attaccetgc cattcatgtg tatcetggta tcatatggct acactggggc
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           481 cgtgttg (SEQ ID NO:292).
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       LOCUS
                   AF179802
                                487 bp DNA
                                                     PRI
                                                            31-DEC-2000
       DEFINITION Macaca sylvanus olfactory receptor (MSY182) gene, partial cds.
       ACCESSION AF179802
       KEYWORDS
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       SOURCE
                    Barbary ape.
        ORGANISM Macaca sylvanus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Catarrhini; Cercopithecidae; Cercopithecinae;
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AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
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       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
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           121 cetecagete gaattetgtg getecaatge cattgateat tttagetgtg atgeaggtee
           181 tetectaaag ateteatget cagacacatg ggtaatagaa cagatagtta taettatgge
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           241 tgtatttgca ctcattatca ccctagtttg tgtgattctg tcctacttgt acatagtcag
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           361 ccacatgatt gtggtttcca ttgcctatgg aagctgcatc ttcgtctata tcaagccctc
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          481 cttgttg (SEQ ID NO:293).
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       OR182
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        ORGANISM Callithrix jacchus
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              Eutheria; Primates; Platyrrhini; Callitrichidae; Callithrix.
       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
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        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
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              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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                                                           31-DEC-2000
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       ACCESSION AF179804
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                   Callithrix jacchus.
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        ORGANISM Callithrix jacchus
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              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Platyrrhini; Callitrichidae; Callithrix.
       REFERENCE 1 (bases 1 to 486)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory receptor gene repertoire in primates and mouse:
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              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 486)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
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        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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       ACCESSION AF179805
       KEYWORDS
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        ORGANISM Callithrix jacchus
             Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
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       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory receptor gene repertoire in primates and mouse:
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             Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 487)
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       ACCESSION AF179806
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              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Platyrrhini; Callitrichidae; Callithrix.
       REFERENCE 1 (bases 1 to 487)
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        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 487)
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        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
15
       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
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Eutheria; Primates; Platyrrhini; Callitrichidae; Callithrix.

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REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
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       REFERENCE 1 (bases 1 to 469)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory receptor gene repertoire in primates and mouse:
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              Evidence for reduction of function in primates
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       REFERENCE 2 (bases 1 to 469)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE Direct Submission
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         JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
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       REFERENCE 1 (bases 1 to 488)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory receptor gene repertoire in primates and mouse:
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              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 488)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
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       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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               The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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        TITLE Direct Submission
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        REFERENCE 1 (bases 1 to 491)
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         AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
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         JOURNAL Unpublished
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         AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
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ORGANISM Pongo pygmaeus

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       REFERENCE 1 (bases 1 to 480)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 480)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
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        REFERENCE 1 (bases 1 to 486)
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                 The olfactory receptor gene repertoire in primates and mouse:
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        REFERENCE 2 (bases 1 to 486)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
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              Evidence for reduction of function in primates
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       ACCESSION AF179816
       KEYWORDS
       SOURCE
                   orangutan.
        ORGANISM Pongo pygmaeus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
15
              Eutheria; Primates; Catarrhini; Hominidae; Pongo.
       REFERENCE 1 (bases 1 to 484)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
20
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 484)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
25
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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                   L" (SEQ ID NO:319).
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                         80 a 142 c 105 g 157 t
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           61 cetggtggcg etgteetggg tgetgaceae etteeatgee atgttacaea etttacteat
           121 ggccaggttg tgtttttgtg cagacaatgt gatcccccac tttttctgtg atatgtctgc
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           181 tetgetgaag etgteetget etgacaeteg agttaatgaa ttggtgatat ttateatggg
           241 agggeteatt ettgteatee eatteetaet eateettggg teetatgeae gaattgtete
           301 ctccatcctc aaggtccctt ctaagggtat ctgcaaggcc ttctctactt gtggctccca
           361 cetetetgtg gtgtecetgt tetatgggae egttagtggt etetaettat geceategge
           421 taatagttet actetgaagg agactgteat ggetgtaatg tacaetgtgg tgacceccat
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           481 gctg (SEQ ID NO:318).
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301 ggctgtcatt cacatgggat ctggagaggg tcgtcggata gctttcacga cctgttcctc

## **OR196**

AF179817 483 bp DNA PRI 31-DEC-2000 LOCUS DEFINITION Pongo pygmaeus olfactory receptor (PPY115) gene, partial cds. 5 ACCESSION AF179817 KEYWORDS SOURCE orangutan. ORGANISM Pongo pygmaeus Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia; 10 Eutheria; Primates; Catarrhini; Hominidae; Pongo. REFERENCE 1 (bases 1 to 483) AUTHORS Giorgi, D.G. and Rouquier, S.P. TITLE The olfactory receptor gene repertoire in primates and mouse: Evidence for reduction of function in primates 15 JOURNAL Unpublished REFERENCE 2 (bases 1 to 483) AUTHORS Giorgi, D.G. and Rouquier, S.P. TITLE Direct Submission JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR 20 1142, rue de la Cardonille, Montpellier Cedex 5 34396, France **FEATURES** Location/Qualifiers source 1..483 /organism="Pongo pygmaeus" /db xref="taxon:9600" 25 <1..>483 gene /gene="PPY115" **CDS** <1..>483 /gene="PPY115" /codon start=1 30 /product="olfactory receptor" /translation="VAVCHPLHYTLIMHGGLCLGLVAGCLVAGFMNSLMETIITFQLL LCHNVINHFACETLAVLRLACVDVSFNKAMVAISGFLVILLPCSLILFSYAHIVAAIL HIPSAQGRRKAFGTCTSHLTVVCMCFGATMFTYMRPAGGSSLEKKNMVALFYAIVIPM L" (SEQ ID NO:321). 35 BASE COUNT 86 a 136 c 115 g 146 t **ORIGIN** 1 gtggccgtct gccacccact gcattacacg ctcatcatgc atggagggct gtgcctgggg 61 ctggtggccg gctgcctggt ggctggtttc atgaattccc tgatggaaac aattatcacc 121 ttccagcttc tcctgtgtca caatgttatt aatcactttg cctgtgagac cttagcagtg 40 181 ctacgactag cetgtgtgga egteteette aacaaggeea tggtggeeat eteagggttt 241 ctggtgatcc tgcttccctg ttcactgatc ctattctcct atgctcacat agttgctgcc 301 attetteata tteettetge eeagggaege egeaaageet ttgggaettg eaegteteae 361 ctcactgtgg tttgcatgtg ctttggggct acaatgttca cctacatgag acctgcgggc 421 ggctcctccc tggaaaagaa gaatatggtt gccctctttt atgccattgt gattccaatg 45 481 ctt (SEQ ID NO:320). **OR197** 31-DEC-2000 **LOCUS** AF179818 484 bp DNA PRI 50 DEFINITION Pongo pygmaeus olfactory receptor (PPY116) gene, partial cds. ACCESSION AF179818 KEYWORDS SOURCE orangutan. ORGANISM Pongo pygmaeus 55 Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;

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Eutheria; Primates; Catarrhini; Hominidae; Pongo.
       REFERENCE 1 (bases 1 to 484)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
 5
              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 484)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
10
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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                   L" (SEQ ID NO:323).
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           61 getggtggee ggetgeetgg tggetggttt catgaattee etgatggaaa caattateae
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          121 cttccagctt cccctgtgtc acaatgttat taatcacttt gcctgtgaga ccttagcagt
          181 gctacgacta gcctgtgtgg acgtctcctt caacaaggcc acggtggcca tctcagggtt
          241 tetggtgate etgetteeet gtteaetgat cetattetee tatgeteaea tagttgetge
          301 cattettegt atteettetg eecagggaca eegeaaagee tttgggacet geaegtetea
          361 cctcactgtg gtttgcatgt gctttggggc tacaatgttc acctacatga gacctgcggg
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          481 gctt (SEQ ID NO:322).
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                              479 bp DNA
                  AF179819
                                                   PRI
                                                          31-DEC-2000
       LOCUS
       DEFINITION Pongo pygmaeus PPY117 pseudogene, partial sequence.
       ACCESSION AF179819
       KEYWORDS
       SOURCE
                   orangutan.
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        ORGANISM Pongo pygmaeus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Catarrhini; Hominidae; Pongo.
       REFERENCE 1 (bases 1 to 479)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
50
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 479)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
55
        TITLE Direct Submission
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JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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           121 tgtgaacctg cetttttgt ggacctaatg tagtagacag ettttttgt gatctteete
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           181 gagtgaccaa acttgcctgc ctggactctt acctcattga aatactaatt gtggtcaata
           241 gtggagttet tteectaage aetttetgte tettggteag etectaeate attattettg
           301 ttatggtttg geteaagtet teggetgeaa tggegaagge attttetaeg etggetteee
           361 atattgcagt agtaatatta ttctttggac cttgcatctt catctatgtg tggcccttta
           421 ccatctatec tttggataaa ettettgeea tattttaeae tgtttteaee eccateeta (SEQ ID NO:324).
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       OR199
                               487 bp DNA
                                                   PRI
                                                           31-DEC-2000
       LOCUS
                  AF179820
       DEFINITION Pongo pygmaeus olfactory receptor (PPY118) gene, partial cds.
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       ACCESSION AF179820
       KEYWORDS
       SOURCE
                   orangutan.
        ORGANISM Pongo pygmaeus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
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              Eutheria; Primates; Catarrhini; Hominidae; Pongo.
       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
35
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
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              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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           181 cctgctcaag ctgtcctgct cagacacctc cctcaatcag ttagcaatct ttacagcagg
           241 attgacagee attatgette catteetgtg cateetggtt tettatggte acattggggt
           301 caccatecte cagattecet ceaccaaggg catatgeaaa geettgteea ettgtggate
           361 ccacctctca gtggtgacta tctattatgg gacaattatt ggtctctatt ttcttcccc
           421 atccagcaac accaatgaca agaacataat tgcttcagtg atatacacag tagtcactcc
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           481 catgttg (SEQ ID NO:325).
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        LOCUS
                   AF179821
                                 475 bp DNA
                                                      PRI
                                                              31-DEC-2000
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        DEFINITION Pongo pygmaeus PPY119 pseudogene, partial sequence.
        ACCESSION AF179821
        KEYWORDS
        SOURCE
                    orangutan.
         ORGANISM Pongo pygmaeus
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               Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
               Eutheria; Primates; Catarrhini; Hominidae; Pongo.
        REFERENCE 1 (bases 1 to 475)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
                 The olfactory receptor gene repertoire in primates and mouse:
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               Evidence for reduction of function in primates
         JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 475)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE Direct Submission
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         JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
               1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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           241 ggtcttatgg gggtgaccat ttttgctttt gctgatctcc tacacggtca ttctgattac
           301 tgtgcagcga cattectcag caggtatgge caaggeteae ageactetga etgeceaeat
           361 tgctgtggtg accgtgttct ttgggccctg tatcttcatc tatgcctggc ctttcagcaa
           421 cttaccagtg gataacattt tgtctgtatt ctctgtagtt ttcacaccta tatta (SEQ ID NO:327).
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        OR201
                   AF179822
                                 487 bp DNA
                                                      PRI
                                                              31-DEC-2000
        DEFINITION Pongo pygmaeus olfactory receptor (PPY120) gene, partial cds.
        ACCESSION AF179822
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KEYWORDS

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SOURCE
                   orangutan.
        ORGANISM Pongo pygmaeus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Catarrhini; Hominidae; Pongo.
 5
       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
10
       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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          181 cetgeteaag etgteetget eagacacete ceteaateag ttageaatet ttaeageagg
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          241 attgacagee attatgette catteetgtg cateetggtt tettatggte acattggggt
          301 caccatecte cagattecet ceaccaaggg catatgeaaa geettgteea ettgtggate
          361 ccacctetea gtggtgacta tetattatgg gacaattatt ggtetetatt ttetteecee
          421 atccagcaac accaatgaca agaacataat tgcttcagtg atatacacag tagtcactcc
          481 catgttg (SEQ ID NO:328).
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       OR202
       LOCUS
                  AF179823
                               487 bp DNA
                                                    PRI
                                                           31-DEC-2000
       DEFINITION Saimiri sciureus olfactory receptor (SSC184) gene, partial cds.
45
       ACCESSION AF179823
       KEYWORDS
                   common squirrel monkey.
       SOURCE
        ORGANISM Saimiri sciureus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
50
              Eutheria; Primates; Platyrrhini; Cebidae; Cebinae; Saimiri.
       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
55
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JOURNAL Unpublished

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REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
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              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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                   ML" (SEQ ID NO:331).
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           481 catgctg (SEQ ID NO:330).
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       LOCUS
                  AF179824
                               488 bp DNA
                                                    PRI
                                                           31-DEC-2000
       DEFINITION Saimiri sciureus olfactory receptor (SSC185) gene, partial cds.
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       ACCESSION AF179824
       KEYWORDS
       SOURCE
                   common squirrel monkey.
        ORGANISM Saimiri sciureus
40
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Platyrrhini; Cebidae; Cebinae; Saimiri.
       REFERENCE 1 (bases 1 to 488)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
45
              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 488)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
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        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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          361 cegtetetet gtggtgtete tgtattatgg etcaatattt ggeeagtace tttteceaac
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                                                  PRI
                                                         31-DEC-2000
       DEFINITION Saimiri sciureus olfactory receptor (SSC186) gene, partial cds.
       ACCESSION AF179825
       KEYWORDS
                  common squirrel monkey.
       SOURCE
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        ORGANISM Saimiri sciureus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
             Eutheria; Primates; Platyrrhini; Cebidae; Cebinae; Saimiri.
       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
35
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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MV" (SEQ ID NO:335).
                         92 a 126 c 105 g 164 t
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        ACCESSION AF179826
        KEYWORDS .
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        ORGANISM Saimiri sciureus
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              Eutheria; Primates; Platyrrhini; Cebidae; Cebinae; Saimiri.
        REFERENCE 1 (bases 1 to 487)
25
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                 The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 487)
30
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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301 etecateete aaggteeett ettetaaggg tatetgeaag geegteteta ettgtggete

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       DEFINITION Saimiri sciureus olfactory receptor (SSC190) gene, partial cds.
       ACCESSION AF179827
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       KEYWORDS
       SOURCE
                   common squirrel monkey.
        ORGANISM Saimiri sciureus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Platyrrhini; Cebidae; Cebinae; Saimiri.
15
       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
20
       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
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           241 gttggtgaca ctcttagtca cattggtaat ggtgataata tcatatactt atattgccct
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          361 teacatgatt gtgatatece tttettatgg cagetgeate tteatgtatg ttaagceate
          421 agtcaaacaa agggtatett tttcaaaggg aattteggtg etcaatacet etgttgetee
          481 acttttg (SEQ ID NO:338).
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                  AF179828
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                                                   PRI
                                                           31-DEC-2000
       DEFINITION Saimiri sciureus olfactory receptor (SSC191) gene, partial cds.
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       ACCESSION AF179828
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361 ccacctetet gtggtgteae tgttetatgg gaetgttatt ggtetetaet tatgeceate 421 agetaataat tetaetetaa aggagaetgt eatggetgtg atgtaeaetg tgatggeeee

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KEYWORDS .
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        ORGANISM Saimiri sciureus
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              Eutheria; Primates; Platyrrhini; Cebidae; Cebinae; Saimiri.
       REFERENCE 1 (bases 1 to 485)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
10
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 485)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
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              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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           361 cacctcactg tagtcataat tttttacaca gccatgattt ttacatatgt tcggcccaga
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                                                           31-DEC-2000
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       DEFINITION Saimiri sciureus olfactory receptor (SSC192) gene, partial cds.
       ACCESSION AF179829
       KEYWORDS
       SOURCE
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        ORGANISM Saimiri sciureus
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              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Platyrrhini; Cebidae; Cebinae; Saimiri.
       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
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Evidence for reduction of function in primates

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JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
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        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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       ACCESSION AF179830
       KEYWORDS
       SOURCE
                   common squirrel monkey.
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        ORGANISM Saimiri sciureus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Platyrrhini; Cebidae; Cebinae; Saimiri.
       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
45
                The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
50
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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       ACCESSION AF179831
       KEYWORDS
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       SOURCE
                   common squirrel monkey.
        ORGANISM Saimiri sciureus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Platyrrhini; Cebidae; Cebinae; Saimiri.
       REFERENCE 1 (bases 1 to 486)
35
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 486)
40
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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                                487 bp DNA
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       ACCESSION AF179832
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       KEYWORDS
       SOURCE
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        ORGANISM Saimiri sciureus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Platyrrhini; Cebidae; Cebinae; Saimiri.
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        REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
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        REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
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           481 catgttt (SEQ ID NO:348).
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                                                             31-DEC-2000
       DEFINITION Saimiri boliviensis SBO213 pseudogene, partial sequence.
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       ACCESSION AF179833
       KEYWORDS
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                    Bolivian squirrel monkey.
        ORGANISM Saimiri boliviensis
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
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              Eutheria; Primates; Platyrrhini; Cebidae; Cebinae; Saimiri.
       REFERENCE 1 (bases 1 to 486)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
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        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 486)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
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              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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       ACCESSION AF179834
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       KEYWORDS
                    Bolivian squirrel monkey.
       SOURCE
        ORGANISM Saimiri boliviensis
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Platyrrhini; Cebidae; Cebinae; Saimiri.
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REFERENCE 1 (bases 1 to 487)

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AUTHORS Giorgi, D.G. and Rouquier, S.P.
               The olfactory receptor gene repertoire in primates and mouse:
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        JOURNAL Unpublished
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       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
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       DEFINITION Saimiri boliviensis olfactory receptor (SBO215) gene, partial cds.
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       ACCESSION AF179835
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                   Bolivian squirrel monkey.
        ORGANISM Saimiri boliviensis
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              Eutheria; Primates; Platyrrhini; Cebidae; Cebinae; Saimiri.
       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
50
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
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              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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       DEFINITION Saimiri boliviensis olfactory receptor (SBO216) gene, partial cds.
       ACCESSION AF179836
       KEYWORDS
                   Bolivian squirrel monkey.
       SOURCE
        ORGANISM Saimiri boliviensis
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              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Platyrrhini; Cebidae; Cebinae; Saimiri.
       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory receptor gene repertoire in primates and mouse:
40
              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
45
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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       LOCUS
                 AF179837
                              487 bp DNA
                                                  PRI
                                                         31-DEC-2000
       DEFINITION Saimiri boliviensis olfactory receptor (SBO217) gene, partial cds.
       ACCESSION AF179837
       KEYWORDS
       SOURCE
                  Bolivian squirrel monkey.
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        ORGANISM Saimiri boliviensis
             Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
             Eutheria; Primates; Platyrrhini; Cebidae; Cebinae; Saimiri.
       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouguier, S.P.
30
                The olfactory receptor gene repertoire in primates and mouse:
             Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
35
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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           481 cacgttg (SEQ ID NO:357).
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                   AF179838
                                486 bp DNA
                                                     PRI
                                                             31-DEC-2000
       DEFINITION Saimiri boliviensis olfactory receptor (SBO218) gene, partial cds.
       ACCESSION AF179838
       KEYWORDS
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       SOURCE
                    Bolivian squirrel monkey.
        ORGANISM Saimiri boliviensis
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Platyrrhini; Cebidae; Cebinae; Saimiri.
       REFERENCE 1 (bases 1 to 486)
20
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
         JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 486)
25
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE Direct Submission
         JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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           481 atgttt (SEQ ID NO:359).
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31-DEC-2000
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                  AF179839
                               487 bp DNA
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       DEFINITION Saimiri boliviensis olfactory receptor (SBO219) gene, partial cds.
       ACCESSION AF179839
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       KEYWORDS
       SOURCE
                   Bolivian squirrel monkey.
        ORGANISM Saimiri boliviensis
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Platyrrhini; Cebidae; Cebinae; Saimiri.
10
       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
        JOURNAL Unpublished
15
       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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           241 tategteatt ettgtgatee eteteattae eactateete teetatatet acattgtete
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           481 catgcta (SEQ ID NO:361).
45
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                               488 bp DNA
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                                                           31-DEC-2000
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                  AF179840
       DEFINITION Saimiri boliviensis SBO220 pseudogene, partial sequence.
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       ACCESSION AF179840
       KEYWORDS
       SOURCE
                   Bolivian squirrel monkey.
        ORGANISM Saimiri boliviensis
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
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              Eutheria; Primates; Platyrrhini; Cebidae; Cebinae; Saimiri.
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REFERENCE 1 (bases 1 to 488)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
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        JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 488)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE Direct Submission
         JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
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              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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           301 gacaatteta aaaateeett caactagtea gaggaaaaag gettttteea egtgttette
           361 teacatgatt gtgatatece tttettatgg eagetgeeat etteatgtat gttaageeat
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           481 cacttttg (SEQ ID NO:363).
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       OR220
                                                     PRI
        LOCUS
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                                487 bp DNA
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        ACCESSION AF179841
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       KEYWORDS
        SOURCE
                    Bolivian squirrel monkey.
         ORGANISM Saimiri boliviensis
               Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Platyrrhini; Cebidae; Cebinae; Saimiri.
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        REFERENCE 1 (bases 1 to 487)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
         JOURNAL Unpublished
45
        REFERENCE 2 (bases 1 to 487)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
         TITLE Direct Submission
         JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
               1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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                              487 bp DNA
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                                                         31-DEC-2000
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       DEFINITION Saimiri boliviensis olfactory receptor (SBO222) gene, partial cds.
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       ACCESSION AF179842
       KEYWORDS
       SOURCE
                  Bolivian squirrel monkey.
        ORGANISM Saimiri boliviensis
             Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
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              Eutheria; Primates; Platyrrhini; Cebidae; Cebinae; Saimiri.
       REFERENCE 1 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE The olfactory receptor gene repertoire in primates and mouse:
              Evidence for reduction of function in primates
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        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
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              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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BASE COUNT

86 a 120 c 105 g 176 t

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       ACCESSION AF179843
       KEYWORDS
       SOURCE
                    Bolivian squirrel monkey.
        ORGANISM Saimiri boliviensis
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              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Primates; Platyrrhini; Cebidae; Cebinae; Saimiri.
       REFERENCE 1 (bases 1 to 487)
         AUTHORS Giorgi, D.G. and Rouquier, S.P.
                The olfactory receptor gene repertoire in primates and mouse:
25
              Evidence for reduction of function in primates
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 487)
        AUTHORS Giorgi, D.G. and Rouquier, S.P.
        TITLE Direct Submission
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        JOURNAL Submitted (24-AUG-1999) Institut de Genetique Humaine, CNRS, UPR
              1142, rue de la Cardonille, Montpellier Cedex 5 34396, France
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           121 getgeggett teettetgea eagaettgga aateeeceae tttttetgeg aacttaatea
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**ORIGIN** 

421 tgcaactggc aactcacatt caagtgctgc agcettggtg atgtacactg tggtcaccec

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LOCUS
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                                                             12-JUL-1999
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        DEFINITION Mus musculus domesticus clone OR1-72M15 olfactory receptor gene,
              partial cds.
        ACCESSION AF073959
        KEYWORDS .
        SOURCE
                    western European house mouse.
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         ORGANISM Mus musculus domesticus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
        REFERENCE 1 (bases 1 to 649)
         AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
15
         TITLE Mouse olfactory receptor genes orthologous to human pseudogenes are
              potentially functional
         JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 649)
         AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
20
        TITLE Direct Submission
        JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS
              UPR 1142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5,
              France
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              Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
15
        TITLE Mouse olfactory receptor genes orthologous to human pseudogenes are
              potentially functional
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
20
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        JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS
              UPR 1142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5,
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12-JUL-1999
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       ACCESSION AF073961
       KEYWORDS
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                   western European house mouse.
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              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
        TITLE Mouse olfactory receptor genes orthologous to human pseudogenes are
15
              potentially functional
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
        TITLE Direct Submission
20
        JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS
              UPR 1142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5,
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                                                            12-JUL-1999
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       ACCESSION AF073962
       KEYWORDS
       SOURCE
                   western European house mouse.
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              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
15
        TITLE Mouse olfactory receptor genes orthologous to human pseudogenes are
              potentially functional
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
20
        TITLE Direct Submission
        JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS
              UPR 1142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5,
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       ACCESSION AF073963
       KEYWORDS .
       SOURCE
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              Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
15
        TITLE Mouse olfactory receptor genes orthologous to human pseudogenes are
              potentially functional
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
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        JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS
              UPR 1142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5,
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       ACCESSION AF073964
       KEYWORDS .
       SOURCE
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              Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
15
                Mouse olfactory receptor genes orthologous to human pseudogenes are
              potentially functional
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
20
        TITLE Direct Submission
        JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS
              UPR 1142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5,
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        ACCESSION AF073965
        KEYWORDS
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               Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
        REFERENCE 1 (bases 1 to 643)
         AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
 15
         TITLE Mouse olfactory receptor genes orthologous to human pseudogenes are
               potentially functional
         JOURNAL Unpublished
        REFERENCE 2 (bases 1 to 643)
         AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
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         TITLE Direct Submission
         JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS
               UPR 1142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5.
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	REFERENCE	1 (bases 1 to 643)	
		Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.	
15	TITLE Mo	TITLE Mouse olfactory receptor genes orthologous to human pseudogenes are	
		potentially functional	
	JOURNAL	IAL Unpublished	
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	JOURNAL	JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS	
		142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5,	
	France		
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		gtat tatgggacag tcatgggcat gtatttccgg ccctgacca gttacagtct	
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LOCUS
                  AF073967
                               649 bp DNA
                                                   ROD
                                                            12-JUL-1999
 5
       DEFINITION Mus musculus domesticus clone OR15-71M24 olfactory receptor gene,
              partial cds.
       ACCESSION AF073967
       KEYWORDS
       SOURCE
                   western European house mouse.
10
        ORGANISM Mus musculus domesticus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
15
        TITLE Mouse olfactory receptor genes orthologous to human pseudogenes are
              potentially functional
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
20
        TITLE Direct Submission
        JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS
              UPR 1142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5,
              France
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                   GPNVIHHFFCDVOPLLTLSCSDTSINELLAFTEGSVVIMSPFILLLSLISIFTRTVLR
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           61 acagagaaag acaatcetet ttgcccagtg ceteacteaa atgtatttet ttgtggettt
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           121 tggtattaca gacagtttcc ttttggctgc gatggccatt gaccgctatg ttgctatttg
           181 caateegett cattacaaca cagteatgag teecaggege tgtegettge tggttgtgge
           241 atcctgggca gtgtcccatc ttcactccct cacccacaca attctcatgg gtcgcctctc
           301 tttctgtgga cccaatgtca ttcatcactt cttttgtgat gtccagccac tgctgacact
           361 etcetgetet gacaceteta teaatgaget ettggeette acagaggget etgttgtaat
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           421 catgagecet tttatettat tgttgtetet tatatetata tteaetegga etgttetgag
           481 ggtcccttca ggggaaggaa ggtacaaagt tttctctacc tgtgggtctc acctcacagt
           541 tgtagcactg ttctatggaa ccataatatc agtgtacatt cgcccctcat ccacctactc
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LOCUS
                   AF073968
                                649 bp DNA
                                                    ROD
                                                             12-JUL-1999
 5
        DEFINITION Mus musculus domesticus clone OR18M olfactory receptor gene,
              partial cds.
        ACCESSION AF073968
       KEYWORDS .
        SOURCE
                    western European house mouse.
10
         ORGANISM Mus musculus domesticus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
       REFERENCE 1 (bases 1 to 649)
         AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
15
         TITLE Mouse olfactory receptor genes orthologous to human pseudogenes are
              potentially functional
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
20
        TITLE Direct Submission
        JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS
              UPR 1142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5.
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           121 tggaagtetg gagatattee ttettgtagt cetggeetat gaeegetatg tggeeatetg
          181 tttacccctt caatattcca gcatcatgag ccccaatctc tgtgtgtgt tggtggtgtt
          241 ctgctgggta tttattgtgt tttatgccat gtttcacaca ctactcttgg ctagattgtc
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          361 ggcatgctct gatgtttata ttaatgaatt aatgatactt atcttgggag ggtttcttct
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          421 tgtcatetca etettaetea teattgtate etatgtaeaa attgteteet eaattttaag
          481 gatttettet actegggeta tecataaget etteteeace tgtggeteae acetgtetgt
          541 ggtctcactg ttctatggga caattattgg tctgtactta tgtccatcag ctaataactc
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LOCUS
                  AF073969
                               649 bp DNA
                                                    ROD
                                                            12-JUL-1999
 5
       DEFINITION Mus musculus domesticus clone OR1M olfactory receptor gene, partial
              cds.
       ACCESSION AF073969
       KEYWORDS
       SOURCE
                   western European house mouse.
10
        ORGANISM Mus musculus domesticus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
15
        TITLE Mouse olfactory receptor genes orthologous to human pseudogenes are
              potentially functional
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
20
        TITLE Direct Submission
        JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS
              UPR 1142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5,
              France
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40
       NO:391).
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                        142 a 161 c 123 g 223 t
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           121 tggagatatg gagagettee ttettgtgge catggeetat gaeegetatg tggeeatetg
           181 etteeetetg cattacacca geateatgag teecaaacte tgtggttgte taatgetget
           241 attgtggatg ctaacaacat cccatgccat gatgcatact ctccttgcag caagattgtc
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           361 ggcttgctca gacacttatg ttaatgagtt gatgatattt ataatgagtt ccctcctcat
50
           421 tgttattcca tttttcctca ttgtcatgtc ttatgcaagg atcattgcct ccattcttaa
           481 ggttccatct attcaaggga tctacaaggt cttctccacc tgtggttccc atctgtctgt
           541 ggtgaccttg ttttatggga caattattgg tetetaetta tgteeateag gtaataatte
           601 cacagtaaag gggactgtca tggccatgat gtacacagtg gtgactccc (SEQ ID NO:390).
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```
LOCUS
                  AF073970
                               649 bp DNA
                                                    ROD
                                                            12-JUL-1999
 5
       DEFINITION Mus musculus domesticus clone OR21M olfactory receptor gene,
              partial cds.
       ACCESSION AF073970
       KEYWORDS
       SOURCE
                   western European house mouse.
10
        ORGANISM Mus musculus domesticus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
15
        TITLE Mouse olfactory receptor genes orthologous to human pseudogenes are
              potentially functional
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
20
        TITLE Direct Submission
        JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS
              UPR 1142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5,
              France
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                   TDLKIPHFVCELNQLVLLACNDTFPNDMVMYFAAILLGGGPLAGILYSYSKIVSSIRA
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                        150 a 156 c 122 g 221 t
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           121 tggagtttta gataactttc ttctagctgt gatggcctat gaccgatatg tggcaatctg
           181 teaccetetg caetatatgg teateatgaa eegeegeete tgtggatttt tagttttggg
           241 gtcttgggtc acaacagcat tgaatteett getgeagagt teaatggeac tgeggetgte
           301 cttttgtaca gacttgaaaa ttccccactt tgtttgtgag cttaatcaac tggtactact
           361 tgcctgtaat gacacettte etaatgacat ggtgatgtae tttgcageta tactgetggg
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           421 tggtggtcct cttgctggca tcctttactc ttattctaag atagtttcct ccatacgtgc
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           541 tgtttcatta ttctattcta cactcttggg tgcgtatctt agttcttctt ttacacaaaa
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LOCUS
                  AF073971
                               649 bp DNA
                                                   ROD
                                                            12-JUL-1999
 5
       DEFINITION Mus musculus domesticus clone OR22M olfactory receptor gene,
              partial cds.
       ACCESSION AF073971
       KEYWORDS
                   western European house mouse.
       SOURCE
10
        ORGANISM Mus musculus domesticus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
15
        TITLE Mouse olfactory receptor genes orthologous to human pseudogenes are
              potentially functional
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
20
        TITLE Direct Submission
        JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS
              UPR 1142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5,
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                        121 a 184 c 140 g 204 t
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          421 tgtcattcca tttgtgctca tccttgtgtc ctatgcacga attgtgtcct ccattctcaa
          481 ggtcccgtct gctcgaggca tccgtaaagc cttctccacc tgtgggtccc acctgtctgt
          541 ggtgtcactg ttctatggga caatcattgg tctgtactta tgtccatcag ctgataactc
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ROD
                                                             12-JUL-1999
       LOCUS
                   AF073972
                               649 bp DNA
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       DEFINITION Mus musculus domesticus clone OR25M olfactory receptor gene,
              partial cds.
       ACCESSION AF073972
       KEYWORDS
       SOURCE
                   western European house mouse.
10
        ORGANISM Mus musculus domesticus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
15
        TITLE Mouse olfactory receptor genes orthologous to human pseudogenes are
              potentially functional
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
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        TITLE Direct Submission
        JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS
              UPR 1142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5,
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       NO:397).
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           361 ggcctgctct gatattcaca ttaatgagtt aatgataatg ataattggag cacttgttgt
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           421 tatactteca tttetaetea teatagtgte ttatgegeae attgteteet ecatteteaa
           481 agtecettea aetegaggea tecacaaggt etteteeaet tgtgggtete atetgtetgt
           541 ggtgtcactg ttctatgggt cagtcattgt tctgtactta tgtccatcat ctaataactc
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LOCUS
                  AF073973
                               649 bp DNA
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                                                            12-JUL-1999
 5
       DEFINITION Mus musculus domesticus clone OR27M olfactory receptor gene,
              partial cds.
       ACCESSION AF073973
       KEYWORDS
       SOURCE
                   western European house mouse.
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        ORGANISM Mus musculus domesticus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
15
        TITLE Mouse olfactory receptor genes orthologous to human pseudogenes are
              potentially functional
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
20
        TITLE Direct Submission
        JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS
              UPR 1142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5,
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           241 gtcctgggca ctgacaacat tgtatgccat gttgcacact ttgctcttaa ctaggttgtc
           301 tttctgtaaa aacaatgtga teececattt tttetgtgac etttetgete teetgaaget
           361 ggcctgctct gatattcaca ttaatgagtt aatgataatg ataattggag cacttgttgt
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           421 tatacttcca tttctactca tcatagtgtc ttatgcgcac attgtctcct ccactctcaa
           481 agreectica actegaggea tecacaaggt etteteeact tgtggttete atetgtetgt
           541 ggtgtcactg ttctatgggt cagtcattgt tctgtactta tgtccatcat ctaataactc
           601 tactgtgaag gatactgtca tgtctatgat gtacactgtg gtgactccc (SEQ ID NO:398).
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LOCUS
                  AF073974
                              649 bp DNA
                                                   ROD
                                                           12-JUL-1999
 5
       DEFINITION Mus musculus domesticus clone OR28M olfactory receptor gene,
             partial cds.
       ACCESSION AF073974
       KEYWORDS
       SOURCE
                   western European house mouse.
10
        ORGANISM Mus musculus domesticus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
15
        TITLE Mouse olfactory receptor genes orthologous to human pseudogenes are
              potentially functional
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
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        TITLE Direct Submission
        JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS
              UPR 1142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5,
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           121 tgggggaact gagtttetgt tgetgactge catggeetat gaeegetatg tggetgtetg
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          241 ctcttggttt gtgggtgtag ttaattctgc tgtggagaca gcagtcacca tgtaccttcc
          301 cacctgtggg cacaatgtac tcaaccatgt ggcctgtgag acactggcac tggtcagact
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LOCUS
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                                                   ROD
                                                            12-JUL-1999
 5
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              partial cds.
       ACCESSION AF073975
       KEYWORDS
       SOURCE
                   western European house mouse.
10
        ORGANISM Mus musculus domesticus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
15
        TITLE Mouse olfactory receptor genes orthologous to human pseudogenes are
              potentially functional
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
20
        TITLE Direct Submission
        JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS
              UPR 1142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5,
              France
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           121 tgctgtttca gagtgtcaca tgctggctgt catggcttat gatcgctatg ttgccatctg
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           241 ggtgtatagt gtaggettga tttgtgecae aggggaaaca gtetgeetge ttagaetget
           301 attetgeaaa getgatgaca taaaceacta ettetgtgat ettttaceae taetggaaca
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           421 tactgtccca getetgacca tecteagtte etacatette ateatageca geatecteeg
           481 catteettee aetgaaggea ggteeaaage etteageace tgeageteee acatettgge
           541 tgttgetgte ttetttgggt etttageatt catgtacett cagecateat cagtcagete
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LOCUS
                  AF073976
                               649 bp DNA
                                                    ROD
                                                            12-JUL-1999
 5
       DEFINITION Mus musculus domesticus clone OR2M olfactory receptor gene, partial
       ACCESSION AF073976
       KEYWORDS
       SOURCE
                   western European house mouse.
10
        ORGANISM Mus musculus domesticus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
15
        TITLE Mouse olfactory receptor genes orthologous to human pseudogenes are
              potentially functional
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
20
        TITLE Direct Submission
        JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS
              UPR 1142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5,
              France
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40
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           121 tggagatett gagagettee teettgtgge eatggeetat gaeegatatg tageeatetg
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          301 tttctgtgaa aacaatgtga tcccccattt tttctgtgat ctgtctgctc tgctgaaget
          361 ggcctgctct gatattcaca ttaatgaatt ggtgatattg atcataggag ggcttgttgt
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          421 tatactteea tttetaeteg teaeagtgte ttatgeaege ateateteet eeatteteaa
          481 ggtcccttca actcgaggca tccacaaggt cttctccact tgtggttctc acctgtctgt
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```
LOCUS
                  AF073977
                               650 bp DNA
                                                    ROD
                                                             12-JUL-1999
 5
       DEFINITION Mus musculus domesticus clone OR3M olfactory receptor gene, partial
       ACCESSION AF073977
       KEYWORDS .
                   western European house mouse.
       SOURCE
10
        ORGANISM Mus musculus domesticus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
       REFERENCE 1 (bases 1 to 650)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
15
        TITLE Mouse olfactory receptor genes orthologous to human pseudogenes are
              potentially functional
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 650)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
20
        TITLE Direct Submission
        JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS
              UPR 1142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5,
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40
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           61 tecaggacae acceatatee tatgtggett gtetgacaea aatgtaettt tteagtgttt
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           121 ttggaagtet ggagatatte ettettgtag teetggeeta tgacegetat gtggeeatet
           181 gtttacccct tcaatattcc agcatcatga gccccaatct ctgtgtgtgt gtggtggtgt
           241 tetgetgggt atttattgtg ttttatgeca tgttteaeae actaetettg getagattgt
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           421 ttgtcacctc actettactc atcattgtat cetatgtaca aattgtetee teaattttaa
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```
LOCUS
                  AF073978
                               648 bp DNA
                                                    ROD
                                                             12-JUL-1999
 5
       DEFINITION Mus musculus domesticus clone OR4M olfactory receptor gene, partial
              cds.
       ACCESSION AF073978
       KEYWORDS .
       SOURCE
                    western European house mouse.
10
        ORGANISM Mus musculus domesticus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
       REFERENCE 1 (bases 1 to 648)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
15
        TITLE Mouse olfactory receptor genes orthologous to human pseudogenes are
              potentially functional
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 648)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
20
        TITLE Direct Submission
        JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS
              UPR 1142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5,
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           121 tgggagtctg gagatattcc ttcttgtagt cctggcctat gaccgctatg tggccatctg
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           241 ctgctgggta tttattgtgt tttatgccat gtttcacaca ctactcttgg ctagattgtc
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           361 ggcatgctct gatgtttata ttaatgaatt aatgatactt atcttgggag ggtttcttct
50
           421 tgtcatetca etettaetea teattgtate etatgtaeaa attgteteet eaattttaag
           481 gatttettet actegggeta tecataaget etteteeace tgtggeteac acetgtetgt
           541 ggtctcactg ttctatggga caattattgg tctgtactta tgtccatcag ctaataactc
           601 tactgaaaag gagactgcca tgtccctgat gtacacagtg gtgactcc (SEQ ID NO:408).
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LOCUS
                   AF073979
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                                                             12-JUL-1999
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       DEFINITION Mus musculus domesticus clone OR5M olfactory receptor gene, partial
              cds.
       ACCESSION AF073979
       KEYWORDS
       SOURCE
                   western European house mouse.
10
        ORGANISM Mus musculus domesticus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
15
        TITLE Mouse olfactory receptor genes orthologous to human pseudogenes are
              potentially functional
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
20
        TITLE Direct Submission
        JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS
              UPR 1142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5,
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           301 attetgtgag gacaatgtga tececeaett tttetgtgae atatetgeee tgeteaagtt
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           421 tgtaateeca tttttaetea ttgttgttte etatgtaeaa attgtetget eeattetaaa
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LOCUS
                  AF073980
                               649 bp DNA
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                                                            12-JUL-1999
 5
       DEFINITION Mus musculus domesticus clone OR6M olfactory receptor gene, partial
       ACCESSION AF073980
       KEYWORDS
       SOURCE
                   western European house mouse.
10
        ORGANISM Mus musculus domesticus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
15
        TITLE Mouse olfactory receptor genes orthologous to human pseudogenes are
              potentially functional
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
20
        TITLE Direct Submission
        JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS
              UPR 1142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5,
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           361 ggcctgctct gatattcaca ttaatgaatt ggtgatattg atcataggag ggcttgttgt
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           421 tatacttcca tttctactcg tcacagtgcc ttatgcacgc atcatctcct ccattctcaa
           481 ggtcccttca actcgaggca tccacaaggt cttctccact tgtggttctc acctgtctgt
           541 ggtgtcactg ttctatggga caattattgg cctctactta tgtccatctg ctaataactc
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LOCUS
                  AF073981
                               649 bp DNA
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                                                             12-JUL-1999
 5
       DEFINITION Mus musculus domesticus clone OR7M olfactory receptor gene, partial
       ACCESSION AF073981
       KEYWORDS
       SOURCE
                   western European house mouse.
10
        ORGANISM Mus musculus domesticus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
15
                 Mouse olfactory receptor genes orthologous to human pseudogenes are
              potentially functional
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
20
        TITLE Direct Submission
        JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS
              UPR 1142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5,
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           361 ggcctgctct gatattcaca ttaatgagtt aatgataatg ataattggag cacttgttgt
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           421 tatacttcca tttctactca tcatagtgtc ttatgcgcac attgtctcct ccattctcaa
           481 agtecettea actegaggea tecacaaggt etteteeact tgtggttete atetgtetge
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                                                            12-JUL-1999
 5
       DEFINITION Mus musculus domesticus clone OR8M olfactory receptor gene, partial
              cds.
       ACCESSION AF073982
       KEYWORDS
       SOURCE
                   western European house mouse.
10
        ORGANISM Mus musculus domesticus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
15
        TITLE Mouse olfactory receptor genes orthologous to human pseudogenes are
              potentially functional
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
20
        TITLE Direct Submission
        JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS
              UPR 1142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5,
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          121 tggagatatg gagagettee ttettgtgge catggeetat gacegetatg tggeeatetg
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          301 tttttgtgag aacaatgtga tcctcaattt tttctgtgac ctatttgtac tcctaaagct
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          541 ggtgaccttg ttttatggga caattattgg tetetaetta tgtecateag gtaataatte
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                  AF073983
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                                                            12-JUL-1999
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              partial cds.
       ACCESSION AF073983
       KEYWORDS
       SOURCE
                   western European house mouse.
10
        ORGANISM Mus musculus domesticus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
15
        TITLE Mouse olfactory receptor genes orthologous to human pseudogenes are
              potentially functional
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
20
        TITLE Direct Submission
        JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS
              UPR 1142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5,
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          121 tgcagaattg gacaactttc tcctggctgt gatggcctat gaccgatatg tggctatctg
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                                                            12-JUL-1999
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       DEFINITION Mus musculus domesticus clone OR912-47M6 olfactory receptor gene,
              partial cds.
       ACCESSION AF073984
       KEYWORDS
                   western European house mouse.
       SOURCE
10
        ORGANISM Mus musculus domesticus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
       REFERENCE 1 (bases 1 to 646)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
15
        TITLE Mouse olfactory receptor genes orthologous to human pseudogenes are
              potentially functional
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 646)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
20
        TITLE Direct Submission
        JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS
              UPR 1142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5,
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           121 tgctgacatg gacaatttcc tgctggctgt gatggcctat gaccgatttg tggccatatg
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           421 gttageteea tttgtttgea teetettgte ttatateett attgettgtg eeateetgaa
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650 bp DNA
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                                                            12-JUL-1999
       LOCUS
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       DEFINITION Mus musculus domesticus clone OR912-47M7 olfactory receptor gene,
              partial cds.
       ACCESSION AF073985
       KEYWORDS .
       SOURCE
                   western European house mouse.
10
        ORGANISM Mus musculus domesticus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
       REFERENCE 1 (bases 1 to 650)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
15
        TITLE Mouse olfactory receptor genes orthologous to human pseudogenes are
              potentially functional
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 650)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
20
        TITLE Direct Submission
        JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS
              UPR 1142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5,
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           121 tggagaactg gacaactttc tcctggctgt gatggcctat gaccgatatg tggctatctg
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                                                            12-JUL-1999
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              partial cds.
       ACCESSION AF073986
       KEYWORDS .
                   western European house mouse.
       SOURCE
10
        ORGANISM Mus musculus domesticus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
15
        TITLE Mouse olfactory receptor genes orthologous to human pseudogenes are
              potentially functional
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
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        TITLE Direct Submission
        JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS
              UPR 1142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5,
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           361 cacatettta gacagetttt caagecacet cataatgaat ettetacete ttetattege
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           421 agteattice ticagtagta teettiacte tiatticaag atagtgteet ceatatgtic
           481 tateteetea gtteaaggga agtacaagge attttetaca tgtgtetete acettteeat
           541 tgtcttctta ttttatagta caggccttgg agtgtatgtc agttctgctg tggtccaaag
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LOCUS
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                                                            12-JUL-1999
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       DEFINITION Mus musculus domesticus clone OR912-47M9 olfactory receptor gene,
              partial cds.
       ACCESSION AF073987
       KEYWORDS .
       SOURCE
                   western European house mouse.
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        ORGANISM Mus musculus domesticus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
15
        TITLE Mouse olfactory receptor genes orthologous to human pseudogenes are
              potentially functional
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
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        TITLE Direct Submission
        JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS
              UPR 1142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5,
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           421 cetageacet gtetecetea tecteacete etaetggaac ateateteca etgtaateea
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           541 tgttgttete ttetaegget eageaatatt tgeetaeatg aggeecaact etaagataat
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       DEFINITION Mus musculus domesticus clone OR9M olfactory receptor gene, partial
       ACCESSION AF073988
       KEYWORDS .
                   western European house mouse.
       SOURCE
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        ORGANISM Mus musculus domesticus
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
       REFERENCE 1 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
15
        TITLE Mouse olfactory receptor genes orthologous to human pseudogenes are
              potentially functional
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 649)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
        TITLE Direct Submission
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        JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS
              UPR 1142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5,
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           241 gtcctggttg ctgaccatgt cccattccat gctgcacact ttgctcttaa ctaggttgtc
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           361 ggcctgctct gatattcaca ttaatgaatt ggtgatattg atcataggag ggcttgttgt
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           421 tatacttcca tttctactcg tcacagtgtc ttatgcacgc atcatctcct ccattctcaa
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           541 ggtgtcactg ttctatggga caattattgg cctctactta tgtccatctg ctaataactc
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## **OR253**

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                  AF073989
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       DEFINITION Mus musculus clone OR1-72M13 olfactory receptor gene, complete cds.
       ACCESSION AF073989
       KEYWORDS
       SOURCE
                   house mouse.
        ORGANISM Mus musculus
10
              Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
              Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
       REFERENCE 1 (bases 1 to 1865)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
        TITLE Mouse olfactory receptor genes orthologous to human pseudogenes are
15
              potentially functional
        JOURNAL Unpublished
       REFERENCE 2 (bases 1 to 1865)
        AUTHORS Giorgi, D.G., Delettre, C. and Rouquier, S.R.P.
        TITLE Direct Submission
20
        JOURNAL Submitted (23-JUN-1998) Institut de Genetique Humaine (IGH), CNRS
              UPR 1142, 141 rue de la Cardonille, Montpellier 34396 Cedex 5,
              France
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                   LLMLRLSFCTNQIIKHFYCEYAKALTIACSDTLINHILLYIVIWVLGFIPFSGILYSY
                   YKIFSSILRIPSTDGKYKAFSTCGSHLSVVSLFYGTGLSVYLSSDATSSSGKGVVASV
40
                   MYTVVTPMLNPFIYSLRNKDIKKALKTLGRILLLK" (SEQ ID NO:431).
                        568 a 355 c 321 g 621 t
       BASE COUNT
       ORIGIN
           1 ctgcagagtg agttctagga cagccaggac tacacagaga aaccctgaat caaaataaaa
           61 taaaataaaa tacaatagaa taaaataaaa taaacaaaaa agaaaaaaga agataaagat
45
           121 gtctaagaga agaatgagat ttcaaaagga atggatacag agaaggtatg gtcatattca
           181 cagagacett tetgaatgat cagaacttag tgtaaceaet gaaaaatgtt gagaagtgaa
           241 gttggaaatc agagttgatc catcataaag gattacagca cttttagaaa ctgactgctt
           301 tgatctaaca cttccagagg ttatctggtc ttcatgtggt ttaaaatttg tagagttagc
           361 agttctaagt agagataagg tagagaaact aataatgatg agaaaatgca ggattcctaa
50
           421 tttttattgt aataaaagct ttatgtacag ttattccaac acataaaagg acagagacct
           481 tagagactgt agtgtatgtt ceteaatett teteteeagt aggtgtetag ettatttgte
           541 aacaacatga aaccagaaaa ccaaacaaaa tattttagaa tttttgcttc tggggttttc
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661 gtgcttggga atcttctcat cattctggcc gtcagcattg actctcacct gcatactccc 721 atgtacttct ttctatctaa cctgtccttt tctgacattg gtttcatctc tacaactgtc 781 cctaagatgt tggtgaatat ccaaacacag agcaagtcca tctcctatgc agaatgcatc 841 acccagattt attitticat getettigga ggeatggaca caetteteet caeegtgatg 901 gcctatgacc gatttgtggc catctgtcac ccacttcact attcagtcat tatgaatcct 5 961 caactaagtg gtttgctagt tcttgtatca tggtttatta gcttttcata ttctctgata 1021 cagagtetat tgatgetgeg gttgteette tgtacaaate agataattaa acaettttae 1081 tgtgaatatg ccaaagccet cactatagce tgeteagata cactaateaa teatateett 1141 ctttatattg tgatatgggt ccttggcttc atccctttct cagggatcct ttattcatac 1201 tataaaattt tttcttcaat tttgagaatt ccatcaacag atggaaaata taaagcattt 10 1261 tetacetgtg ggteteatet ateggtggtt tetttattet atgggacagg cettagtgtg 1321 taccttagtt ctgatgctac ttcctcctct gggaagggcg tggtggcctc agtaatgtat 1381 acagtggtca cccccatgct gaaccetttc atctacagct tgaggaacaa agacattaag 1441 aaggeettaa aaacaettgg gagaataett ettttaaagt gataatttea etggttttag 1501 acatetgaac tgatagaaat aaaatagtga actaaagaaa ttetgtacta taateatgta 15 1561 gaaattttat ccagtttgtt ggtctatctt tgattaaaat tatactgtga atatttctat 1621 etgaaattte tatgatgeet eetttttat tegaagttet ttgteteete eeetgtttta 1681 tacgacatat ttctttactt cagtacaaag tctacatttc agcatgccaa tataaccatt 1741 caaataccaa ttcatgaatt gtttagtaaa agttatgcaa tggctcattt acagaaagtc 20 1801 catgtatata tatataacac tgttgtgggt tggtccgact ctgtattctg atattaattc 1861 tgcag (SEQ ID NO:430).

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As used herein, the terms "ORX nucleic acid sequence" and/or "ORX nucleic acid molecule" specifically refer to the sequences of GenBank Accession Nos. AF022649, AF073959-073989, AF127814-127907, and AF179716-179843.

Likewise, the term "ORX polypeptide" specifically refers to the polypeptide sequences of GenBank Accession Nos. AF127814, AF127816-127819, AF127821-127824, AF127836-127837, AF127840, AF127845-127848, AF127851-127852, AF127857, AF127859, AF127861-127862, AF127865, AF127867-127868, AF127870-127872, AF127874-127884, AF127886, AF127888, AF127896-127904, AF127906-127907, AF179716-179717, AF179720-179728, AF179730-179737, AF179739-179746, AF179748-179750, AF179752, AF179755-179756, AF179758-179761, AF179766-179767, AF179770-179771, AF179773-179775, AF179777-179779, AF179784-179788, AF179790-179792, AF179794, AF179796-179799, AF179802-179811, AF179814, AF179816-179818, AF179820, AF179822-179832, AF179834-179839, AF179841-179843, and AF073959-073989.

To sample the ORX genes in primate species, ORX genes were randomly sequenced from anthropoids and prosimians (See FIG. 1). As outlined in Examples 1-3, infra, ORX genes were obtained by PCR on genomic DNA from the different species using consensus ORX primer pairs OR5B-OR3B and OR3.1-OR7.1 chosen respectively in the transmembrane

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individual ORX clones were sequenced per taxon. A total of 221 ORX sequences, representing ten species, was analyzed. These sequences are distributed in different groups whose percentage of nucleotide sequence identity (NSI) ranges from ~35 to >99%. The corresponding amino acid sequences were compared to a variety of ORX sequences from the public databases and previous studies. See Rouquier et al., (1998) Nature Genet. 18, 243-50.

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All sequences have the characteristic features of olfactory receptors, with a heptahelical structure and conserved motifs as previously defined. See Buck et al., (1991) Cell 65, 175-187; Rouquier et al., (1998) Nature Genet. 18, 243-50; and Rouquier et al., (1998) Hum. Mol. Genet. 7, 1337-45. The use of two pairs of consensus primers made the sampling representative of the ORX gene repertoire. Primate sequences are distributed in seven families (sequences that share >40% amino-acid identity (ASI) define a family), and 56 subfamilies (sequences that share >60% ASI define a subfamily). Group 1-II of family 1 represents the zone of overlap of sequences derived from using the two primer pairs (See FIG. 2).

Non-human primate ORX genes are represented in 6 families and about 45 subfamilies. Numerous sequences are grouped in family 1 (~66%) comprising subfamily 1A, the largest subfamily (57/221, 26%). Subfamily 1B is almost devoid of coding human ORX sequences (FIG. 2). Subfamily 1A contains only human pseudogenes originating from chromosomes 14 and 19 whereas subfamily 1B contains human pseudogenes lying on various chromosomes. As has been previously found for human, the amino-acid sequences deduced from the non-human primate sequences revealed many pseudogenes (FIG. 2 and Table 1).

Table 1 provides information about the evolution of the pseudogene fraction along with the evolution of primates. Hominoids present the highest fraction of pseudogenes (39 to >70%, average ~50%). Old world monkeys (macaque and baboon) have a lower pseudogene fraction (20 to 35%, average 27%), while even fewer pseudogenes were found among the sequences derived from new world monkeys. Only one pseudogene (SBO64) was identified among the 49 sequences obtained from marmoset and two species of squirrel-monkey. In contrast, 37% of the prosimian lemur ORX sequences were pseudogenes.

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TABLE 1

	Species					
	Common name		Number of sequences analyzed	% ORF	% pseudogenes	Average % pseudogenes
	Human	Homo sapiens (HSA)	66	30	70	0
	Chimpanzee	Pan troglodytes (PTR)	21	52	48	
Hominoids	Gorilla	Gorilla gorilla (GGO)	18	50	50	% 05
	Orangutan	Pongo pygmaeus (PPY)	23	19	39	
	Gibbon	Hylobates lar (HLA)	22	59	41	
Old world monkeys	Macaque	Macaca sylvanus (MSY) 20	20	9	35	
	Baboon	Papio papio (PPA)	21	81	19	27 %
	Marmoset	Callithrix jacchus (CJA)	19	001	0	
New world monkeys	Squirrel-monkey	Saimiri scireus (SSC)	15	100	0	2 %
·		Saimiri bolivensis (SBO)	15	93	7	

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Frosimians	Lemur	Eulemur fulvus (EFU)		58	42	
		Eulemur rubriventer (ERU)	16	69	31	37 %
Rodents	Mouse	Mus musculus (MMU) 33		100	0	% 0
Fish	Zebrafish	Danio rerio (DRE)	3	100	0	% 0

Diverse reasons have been suggested that could account for the differences in olfactory ability among mammals, *i.e.*, the size of the anatomical structures devoted to olfaction (olfactory epithelium, olfactory bulb, cortical structures), or the number of ORX families/subfamilies, and the total number and diversity of expressed ORX genes. The olfactory epithelial surface of macrosmatic animals, such as dogs, is larger than in microsmatic humans. On the other hand, using unique dog sequence probes that represent specific ORX subfamilies and which will not cross-hybridize with other subfamilies, comparative analyses have been performed by Southern blot analysis among a panel of mammals including dog and human. The number of ORX sequences per subfamily is similar in microsmatic and macrosmatic animals. A high fraction (>70%) of the human ORX genes have been mutated during evolution into pseudogenes. Chromosomes 7, 16 or 17 contained a high fraction of potentially coding ORX sequences, whereas other chromosomes such as chromosome 3 or 11 contained primarily pseudogenes. Other studies on chromosome 17 and on chromosome 11 in which 75% of the ORX sequences identified were pseudogenes, support these observations.

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All ORX sequences derived from mouse are potentially coding. No pseudogenes were detected either by sequencing randomly selected ORX sequences or by deliberately screening with human ORX pseudogene probes. This indicates that the ORX pseudogene content is either zero or restricted to rare examples in mouse.

Thus, the reduction of the sense of smell could correlate with the fraction of functional ORX genes in the genome.

It is difficult to measure and compare the olfactory efficiency of different animal species. Various parameters such as the threshold of detection of odorants (sensitivity), the range of odors detectable and the discriminatory power (acuity) are key parts of the olfactory ability. Thus it is uncertain to determine precisely which of these parameters are taken in account when comparing two species, and therefore the origin of the olfactory deficiency of primates remains a controversial and difficult point to address.

The chromosomal distribution of the ORX gene repertoire arose through multiple duplication rounds giving rise to paralogous regions. Even though the number of duplication events may be different among the mammals, overall it appears that the number of ORX genes was established before the divergence of mammals. See Ben-Arie et al., (1994) Hum. Mol. Genet. 3, 229-35. This explains why, by Southern analysis, there is no striking difference in the

number of ORX genes of four different subfamilies between the sea lion, which has an underdeveloped olfactory apparatus, and other mammals. See id. On the other hand, the Southern blot approach does not reveal the functionality of the ORX sequences, and we predict that a large fraction of the sea lion ORX genes could be pseudogenes as has been described for the dolphin. See Sharon et al., (1999) Genomics, 61, 24-36. Similarly striking differences have been observed in the olfactory ability of different breeds of dogs. See Issel-Tarver et al., (1996) Proc. Natl. Acad. Sci. USA 93, 10897-902. Despite the variations in the size of the olfactory epithelium of the different breeds, it would be interesting to know what the biological basis is for the differences in performances observed between sight and scent hounds. One obvious possibility is loss of functional ORX genes, but, given the recent origin of all modern dogs this explanation seems unlikely. Other explanations could be changes in behavior, or in expression brought about by the modification of a key master transcription factor or in the unusual mechanism that allows only one ORX gene allele or the other to be expressed exclusively in any one epithelium cell.

# **ORX Nucleic Acids**

The nucleic acids of the invention include those that encode an ORX polypeptide or protein. As used herein, the terms polypeptide and protein are interchangeable.

In some embodiments, an ORX nucleic acid encodes a mature ORX polypeptide. As used herein, a "mature" form of a polypeptide or protein described herein relates to the product of a naturally occurring polypeptide or precursor form or proprotein. The naturally occurring polypeptide, precursor or proprotein includes, by way of nonlimiting example, the full-length gene product, encoded by the corresponding gene. Alternatively, it may be defined as the polypeptide, precursor or proprotein encoded by an open reading frame described herein. The product "mature" form arises, again by way of nonlimiting example, as a result of one or more naturally occurring processing steps that may take place within the cell in which the gene product arises. Examples of such processing steps leading to a "mature" form of a polypeptide or protein include the cleavage of the N-terminal methionine residue encoded by the initiation codon of an open reading frame, or the proteolytic cleavage of a signal peptide or leader sequence. Thus a mature form arising from a precursor polypeptide or protein that has residues 1 to N, where residue 1 is the N-terminal methionine, would have residues 2 through N remaining after removal

of the N-terminal methionine. Alternatively, a mature form arising from a precursor polypeptide or protein having residues 1 to N, in which an N-terminal signal sequence from residue 1 to residue M is cleaved, would have the residues from residue M+1 to residue N remaining. Further as used herein, a "mature" form of a polypeptide or protein may arise from a step of post-translational modification other than a proteolytic cleavage event. Such additional processes include, by way of non-limiting example, glycosylation, myristoylation or phosphorylation. In general, a mature polypeptide or protein may result from the operation of only one of these processes, or a combination of any of them.

Among the ORX nucleic acids is the nucleic acid whose sequence is provided by GenBank Accession Numbers AF022649, AF073959-073989, AF127814-127907, and AF179716-179843, or a fragment thereof. Additionally, the invention includes mutant or variant nucleic acids of GenBank Accession Numbers AF022649, AF073959-073989, AF127814-127907, and AF179716-179843, or a fragment thereof, any of whose bases may be changed from the corresponding bases shown in the ORX nucleic acids, while still encoding a protein that maintains at least one of its ORX-like activities and physiological functions (*i.e.*, modulating angiogenesis, neuronal development). The invention further includes the complement of the nucleic acid sequence of GenBank Accession Numbers AF022649, AF073959-073989, AF127814-127907, and AF179716-179843, including fragments, derivatives, analogs and homologs thereof. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications.

One aspect of the invention pertains to isolated nucleic acid molecules that encode ORX proteins or biologically active portions thereof. Also included are nucleic acid fragments sufficient for use as hybridization probes to identify ORX-encoding nucleic acids (e.g., ORX mRNA) and fragments for use as polymerase chain reaction (PCR) primers for the amplification or mutation of ORX nucleic acid molecules. As used herein, the term "nucleic acid molecule" is intended to include DNA molecules (e.g., cDNA or genomic DNA), RNA molecules (e.g., mRNA), analogs of the DNA or RNA generated using nucleotide analogs, and derivatives, fragments and homologs thereof. The nucleic acid molecule can be single-stranded or double-stranded, but preferably is double-stranded DNA.

"Probes" refer to nucleic acid sequences of variable length, preferably between at least about 10 nucleotides (nt), 100 nt, or as many as about, e.g., 6,000 nt, depending on use. Probes

are used in the detection of identical, similar, or complementary nucleic acid sequences. Longer length probes are usually obtained from a natural or recombinant source, are highly specific and much slower to hybridize than oligomers. Probes may be single- or double-stranded and designed to have specificity in PCR, membrane-based hybridization technologies, or ELISA-like technologies.

An "isolated" nucleic acid molecule is one that is separated from other nucleic acid molecules that are present in the natural source of the nucleic acid. Examples of isolated nucleic acid molecules include, but are not limited to, recombinant DNA molecules contained in a vector, recombinant DNA molecules maintained in a heterologous host cell, partially or substantially purified nucleic acid molecules, and synthetic DNA or RNA molecules. Preferably, an "isolated" nucleic acid is free of sequences which naturally flank the nucleic acid (*i.e.*, sequences located at the 5' and 3' ends of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. For example, in various embodiments, the isolated ORX nucleic acid molecule can contain less than about 50 kb, 25 kb, 5 kb, 4 kb, 3 kb, 2 kb, 1 kb, 0.5 kb or 0.1 kb of nucleotide sequences which naturally flank the nucleic acid molecule in genomic DNA of the cell from which the nucleic acid is derived. Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material or culture medium when produced by recombinant techniques, or of chemical precursors or other chemicals when chemically synthesized.

A nucleic acid molecule of the present invention, *e.g.*, a nucleic acid molecule having the nucleotide sequence of GenBank Accession Numbers AF022649, AF073959-073989, AF127814-127907, and AF179716-179843, or a complement of any of these nucleotide sequences, can be isolated using standard molecular biology techniques and the sequence information provided herein. Using all or a portion of the nucleic acid sequence of GenBank Accession Numbers AF022649, AF073959-073989, AF127814-127907, and AF179716-179843, as a hybridization probe, ORX nucleic acid sequences can be isolated using standard hybridization and cloning techniques (*e.g.*, as described in Sambrook *et al.*, eds., MOLECULAR CLONING: A LABORATORY MANUAL 2<sup>nd</sup> Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989; and Ausubel, *et al.*, eds., CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, New York, NY, 1993.)

A nucleic acid of the invention can be amplified using cDNA, mRNA or alternatively, genomic DNA, as a template and appropriate oligonucleotide primers according to standard PCR amplification techniques. The nucleic acid so amplified can be cloned into an appropriate vector and characterized by DNA sequence analysis. Furthermore, oligonucleotides corresponding to ORX nucleotide sequences can be prepared by standard synthetic techniques, *e.g.*, using an automated DNA synthesizer.

As used herein, the term "oligonucleotide" refers to a series of linked nucleotide residues, which oligonucleotide has a sufficient number of nucleotide bases to be used in a PCR reaction. A short oligonucleotide sequence may be based on, or designed from, a genomic or cDNA sequence and is used to amplify, confirm, or reveal the presence of an identical, similar or complementary DNA or RNA in a particular cell or tissue. Oligonucleotides comprise portions of a nucleic acid sequence having about 10 nt, 50 nt, or 100 nt in length, preferably about 15 nt to 30 nt in length. In one embodiment, an oligonucleotide comprising a nucleic acid molecule less than 100 nt in length would further comprise at lease 6 contiguous nucleotides of GenBank Accession Numbers AF022649, AF073959-073989, AF127814-127907, and AF179716-179843, or a complement thereof. Oligonucleotides may be chemically synthesized and may be used as probes.

In another embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule that is a complement of the nucleotide sequences shown in GenBank Accession Numbers AF022649, AF073959-073989, AF127814-127907, and AF179716-179843, or a portion of this nucleotide sequence. A nucleic acid molecule that is complementary to the nucleotide sequences shown in GenBank Accession Numbers AF022649, AF073959-073989, AF127814-127907, and AF179716-179843 is one that is sufficiently complementary to the nucleotide sequences shown in GenBank Accession Numbers AF022649, AF073959-073989, AF127814-127907, and AF179716-179843 that it can hydrogen bond with little or no mismatches to the nucleotide sequences shown in GenBank Accession Numbers AF022649, AF073959-073989, AF127814-127907, and AF179716-179843, thereby forming a stable duplex.

As used herein, the term "complementary" refers to Watson-Crick or Hoogsteen base pairing between nucleotide units of a nucleic acid molecule, and the term "binding" means the physical or chemical interaction between two polypeptides or compounds or associated polypeptides or compounds or combinations thereof. Binding includes ionic, non-ionic, Von der

Waals, hydrophobic interactions, etc. A physical interaction can be either direct or indirect. Indirect interactions may be through or due to the effects of another polypeptide or compound. Direct binding refers to interactions that do not take place through, or due to, the effect of another polypeptide or compound, but instead are without other substantial chemical intermediates.

Moreover, the nucleic acid molecule of the invention can comprise only a portion of the nucleic acid sequence of GenBank Accession Numbers AF022649, AF073959-073989, AF127814-127907, and AF179716-179843, e.g., a fragment that can be used as a probe or primer, or a fragment encoding a biologically active portion of ORX. Fragments provided herein are defined as sequences of at least 6 (contiguous) nucleic acids or at least 4 (contiguous) amino acids, a length sufficient to allow for specific hybridization in the case of nucleic acids or for specific recognition of an epitope in the case of amino acids, respectively, and are at most some portion less than a full length sequence. Fragments may be derived from any contiguous portion of a nucleic acid or amino acid sequence of choice. Derivatives are nucleic acid sequences or amino acid sequences formed from the native compounds either directly or by modification or partial substitution. Analogs are nucleic acid sequences or amino acid sequences that have a structure similar to, but not identical to, the native compound but differs from it in respect to certain components or side chains. Analogs may be synthetic or from a different evolutionary origin and may have a similar or opposite metabolic activity compared to wild type.

Derivatives and analogs may be full length or other than full length, if the derivative or analog contains a modified nucleic acid or amino acid, as described below. Derivatives or analogs of the nucleic acids or proteins of the invention include, but are not limited to, molecules comprising regions that are substantially homologous to the nucleic acids or proteins of the invention, in various embodiments, by at least about 70%, 80%, 85%, 90%, 95%, 98%, or even 99% identity (with a preferred identity of 80-99%) over a nucleic acid or amino acid sequence of identical size or when compared to an aligned sequence in which the alignment is done by a computer homology program known in the art, or whose encoding nucleic acid is capable of hybridizing to the complement of a sequence encoding the aforementioned proteins under stringent, moderately stringent, or low stringent conditions. See e.g. Ausubel, et al., CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, New York, NY, 1993, and below. An exemplary program is the Gap program (Wisconsin Sequence Analysis Package, Version 8 for UNIX, Genetics Computer Group, University Research Park, Madison, WI) using the default

settings, which uses the algorithm of Smith and Waterman (Adv. Appl. Math., 1981, 2: 482-489, which is incorporated herein by reference in its entirety).

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A "homologous nucleic acid sequence" or "homologous amino acid sequence," or variations thereof, refer to sequences characterized by a homology at the nucleotide level or amino acid level as discussed above. Homologous nucleotide sequences encode those sequences coding for isoforms of an ORX polypeptide. Isoforms can be expressed in different tissues of the same organism as a result of, for example, alternative splicing of RNA. Alternatively, isoforms can be encoded by different genes. In the present invention, homologous nucleotide sequences include nucleotide sequences encoding for an ORX polypeptide of species other than humans, including, but not limited to, mammals, and thus can include, e.g., mouse, rat, rabbit, dog, cat cow, horse, and other organisms. Homologous nucleotide sequences also include, but are not limited to, naturally occurring allelic variations and mutations of the nucleotide sequences set forth herein. A homologous nucleotide sequence does not, however, include the nucleotide sequence encoding human ORX protein. Homologous nucleic acid sequences include those nucleic acid sequences that encode conservative amino acid substitutions (see below) in the amino acid sequence of an ORX polypeptide, as well as a polypeptide having ORX activity. Biological activities of the ORX proteins are described below. A homologous amino acid sequence does not encode the amino acid sequence of a human ORX polypeptide.

The nucleotide sequence determined from the cloning of the human ORX gene allows for the generation of probes and primers designed for use in identifying and/or cloning ORX homologues in other cell types, *e.g.*, from other tissues, as well as ORX homologues from other mammals. The probe/primer typically comprises a substantially purified oligonucleotide. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12, 25, 50, 100, 150, 200, 250, 300, 350 or 400 or more consecutive sense strand nucleotide sequences of GenBank Accession Numbers AF022649, AF073959-073989, AF127814-127907, and AF179716-179843; or an anti-sense strand nucleotide sequence of GenBank Accession Numbers AF022649, AF073959-073989, AF127814-127907, and AF179716-179843; or of a naturally occurring mutant of GenBank Accession Numbers AF022649, AF073959-073989, AF127814-127907, and AF179716-179843.

Probes based on the human ORX nucleotide sequence can be used to detect transcripts or genomic sequences encoding the same or homologous proteins. In various embodiments, the

probe further comprises a label group attached thereto, e.g., the label group can be a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used as a part of a diagnostic test kit for identifying cells or tissue which misexpress an ORX protein, such as by measuring a level of an ORX-encoding nucleic acid in a sample of cells from a subject e.g., detecting ORX mRNA levels or determining whether a genomic ORX gene has been mutated or deleted.

A "polypeptide having a biologically active portion of ORX" refers to polypeptides exhibiting activity similar, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. A nucleic acid fragment encoding a "biologically active portion of ORX" can be prepared by isolating a portion of an ORX nucleic acid that encodes a polypeptide having an ORX biological activity (biological activities of the ORX proteins are described below), expressing the encoded portion of ORX protein (e.g., by recombinant expression in vitro) and assessing the activity of the encoded portion of ORX. For example, a nucleic acid fragment encoding a biologically active portion of ORX can optionally include an ATP-binding domain. In another embodiment, a nucleic acid fragment encoding a biologically active portion of ORX includes one or more regions.

# **ORX** Variants

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The invention further encompasses nucleic acid molecules that differ from the nucleotide sequences shown in GenBank Accession Numbers AF022649, AF073959-073989, AF127814-127907, and AF179716-179843 due to the degeneracy of the genetic code. These nucleic acid molecules thus encode the same ORX protein as that encoded by the nucleotide sequences shown in GenBank Accession Numbers AF022649, AF073959-073989, AF127814-127907, and AF179716-179843 *e.g.*, the ORX polypeptides.

In addition to the human ORX nucleic acids, it will be appreciated by those skilled in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequences of ORX may exist within a population (e.g., the human population). Such genetic polymorphism in the ORX gene may exist among individuals within a population due to natural allelic variation. As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules comprising an open reading frame encoding an ORX protein, preferably a mammalian ORX protein. Such

natural allelic variations can typically result in 1-5% variance in the nucleotide sequence of the ORX gene. Any and all such nucleotide variations and resulting amino acid polymorphisms in ORX that are the result of natural allelic variation and that do not alter the functional activity of ORX are intended to be within the scope of the invention.

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Moreover, nucleic acid molecules encoding ORX proteins from other species, and thus that have a nucleotide sequence that differs from the human sequence of the ORX nucleic acid molecules are intended to be within the scope of the invention. Nucleic acid molecules corresponding to natural allelic variants and homologues of the ORX cDNAs of the invention can be isolated based on their homology to the human ORX nucleic acids disclosed herein using the human cDNAs, or a portion thereof, as a hybridization probe according to standard hybridization techniques under stringent hybridization conditions. For example, a soluble human ORX cDNA can be isolated based on its homology to human membrane-bound ORX. Likewise, a membrane-bound human ORX cDNA can be isolated based on its homology to soluble human ORX.

Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 6 nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence of GenBank Accession Numbers AF022649, AF073959-073989, AF127814-127907, and AF179716-179843. In another embodiment, the nucleic acid is at least 10, 25, 50, 100, 250, 500 or 750 nucleotides in length. In another embodiment, an isolated nucleic acid molecule of the invention hybridizes to the coding region. As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences at least 60% homologous to each other typically remain hybridized to each other.

Homologs (i.e., nucleic acids encoding ORX proteins derived from species other than human) or other related sequences (e.g., paralogs) can be obtained by low, moderate or high stringency hybridization with all or a portion of the particular human sequence as a probe using methods well known in the art for nucleic acid hybridization and cloning.

As used herein, the phrase "stringent hybridization conditions" refers to conditions under which a probe, primer or oligonucleotide will hybridize to its target sequence, but to no other sequences. Stringent conditions are sequence-dependent and will be different in different circumstances. Longer sequences hybridize specifically at higher temperatures than shorter

sequences. Generally, stringent conditions are selected to be about 5 °C lower than the thermal melting point (T<sub>m</sub>) for the specific sequence at a defined ionic strength and pH. The Tm is the temperature (under defined ionic strength, pH and nucleic acid concentration) at which 50% of the probes complementary to the target sequence hybridize to the target sequence at equilibrium. Since the target sequences are generally present at excess, at Tm, 50% of the probes are occupied at equilibrium. Typically, stringent conditions will be those in which the salt concentration is less than about 1.0 M sodium ion, typically about 0.01 to 1.0 M sodium ion (or other salts) at pH 7.0 to 8.3 and the temperature is at least about 30 °C for short probes, primers or oligonucleotides (e.g., 10 nt to 50 nt) and at least about 60°C for longer probes, primers and oligonucleotides. Stringent conditions may also be achieved with the addition of destabilizing agents, such as formamide.

Stringent conditions are known to those skilled in the art and can be found in CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. Preferably, the conditions are such that sequences at least about 65%, 70%, 75%, 85%, 90%, 95%, 98%, or 99% homologous to each other typically remain hybridized to each other. A non-limiting example of stringent hybridization conditions is hybridization in a high salt buffer comprising 6X SSC, 50 mM Tris-HCl (pH 7.5), 1 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.02% BSA, and 500 mg/ml denatured salmon sperm DNA at 65 °C. This hybridization is followed by one or more washes in 0.2X SSC, 0.01% BSA at 50 °C. An isolated nucleic acid molecule of the invention that hybridizes under stringent conditions to the sequence of GenBank Accession Numbers AF022649, AF073959-073989, AF127814-127907, and AF179716-179843 corresponds to a naturally occurring nucleic acid molecule. As used herein, a "naturally-occurring" nucleic acid molecule refers to an RNA or DNA molecule having a nucleotide sequence that occurs in nature (e.g., encodes a natural protein).

In a second embodiment, a nucleic acid sequence that is hybridizable to the nucleic acid molecule comprising the nucleotide sequence of GenBank Accession Numbers AF022649, AF073959-073989, AF127814-127907, and AF179716-179843, or fragments, analogs or derivatives thereof, under conditions of moderate stringency is provided. A non-limiting example of moderate stringency hybridization conditions are hybridization in 6X SSC, 5X Denhardt's solution, 0.5% SDS and 100 mg/ml denatured salmon sperm DNA at 55°C, followed by one or more washes in 1X SSC, 0.1% SDS at 37 °C. Other conditions of moderate stringency

that may be used are well known in the art. See, e.g., Ausubel et al. (eds.), 1993, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, NY, and Kriegler, 1990, GENE TRANSFER AND EXPRESSION, A LABORATORY MANUAL, Stockton Press, NY.

In a third embodiment, a nucleic acid that is hybridizable to the nucleic acid molecule comprising the nucleotide sequence of GenBank Accession Numbers AF022649, AF073959-073989, AF127814-127907, and AF179716-179843, or fragments, analogs or derivatives thereof, under conditions of low stringency, is provided. A non-limiting example of low stringency hybridization conditions are hybridization in 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 mg/ml denatured salmon sperm DNA, 10% (wt/vol) dextran sulfate at 40 °C, followed by one or more washes in 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS at 50 °C. Other conditions of low stringency that may be used are well known in the art (e.g., as employed for cross-species hybridizations). See, e.g., Ausubel et al. (eds.), 1993, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, NY, and Kriegler, 1990, GENE TRANSFER AND EXPRESSION, A LABORATORY MANUAL, Stockton Press, NY; Shilo and Weinberg, 1981, *Proc Natl Acad Sci USA* 78: 6789-6792.

#### **Conservative mutations**

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In addition to naturally-occurring allelic variants of the ORX sequence that may exist in the population, the skilled artisan will further appreciate that changes can be introduced by mutation into the nucleotide sequence of the ORX nucleic acid molecules, thereby leading to changes in the amino acid sequence of the encoded ORX protein, without altering the functional ability of the ORX protein. For example, nucleotide substitutions leading to amino acid substitutions at "non-essential" amino acid residues can be made in the sequence of GenBank Accession Numbers AF022649, AF073959-073989, AF127814-127907, and AF179716-179843. A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequence of ORX without altering the biological activity, whereas an "essential" amino acid residue is required for biological activity. For example, amino acid residues that are conserved among the ORX proteins of the present invention, are predicted to be particularly unamenable to alteration.

Another aspect of the invention pertains to nucleic acid molecules encoding ORX proteins that contain changes in amino acid residues that are not essential for activity. Such ORX

proteins differ in amino acid sequence from the ORX polypeptides, yet retain biological activity. In one embodiment, the isolated nucleic acid molecule comprises a nucleotide sequence encoding a protein, wherein the protein comprises an amino acid sequence at least about 75% homologous to the amino acid sequence of the ORX polypeptides. Preferably, the protein encoded by the nucleic acid is at least about 80% homologous to the sequence of an ORX polypeptide, more preferably at least about 90%, 95%, 98%, and most preferably at least about 99% homologous to the sequence of an ORX polypeptide.

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An isolated nucleic acid molecule encoding an ORX protein homologous to the protein of can be created by introducing one or more nucleotide substitutions, additions or deletions into the nucleotide sequence of GenBank Accession Numbers AF022649, AF073959-073989, AF127814-127907, and AF179716-179843, such that one or more amino acid substitutions, additions or deletions are introduced into the encoded protein.

Mutations can be introduced into the nucleotide sequence of the ORX nucleic acid molecules by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted nonessential amino acid residue in ORX is replaced with another amino acid residue from the same side chain family. Alternatively, in another embodiment, mutations can be introduced randomly along all or part of an ORX coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for ORX biological activity to identify mutants that retain activity. Following mutagenesis of the ORX nucleic acid molecule, the encoded protein can be expressed by any recombinant technology known in the art and the activity of the protein can be determined.

In one embodiment, a mutant ORX protein can be assayed for (1) the ability to form protein:protein interactions with other ORX proteins, other cell-surface proteins, or biologically active portions thereof, (2) complex formation between a mutant ORX protein and an ORX receptor; (3) the ability of a mutant ORX protein to bind to an intracellular target protein or biologically active portion thereof; (e.g., avidin proteins); (4) the ability to bind ORX protein; or (5) the ability to specifically bind an anti-ORX protein antibody.

#### **Antisense ORX Nucleic Acids**

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Another aspect of the invention pertains to isolated antisense nucleic acid molecules that are hybridizable to or complementary to the nucleic acid molecule comprising the nucleotide sequence of the ORX nucleic acid molecule, or fragments, analogs or derivatives thereof. An "antisense" nucleic acid comprises a nucleotide sequence that is complementary to a "sense" nucleic acid encoding a protein, *e.g.*, complementary to the coding strand of a double-stranded cDNA molecule or complementary to an mRNA sequence. In specific aspects, antisense nucleic acid molecules are provided that comprise a sequence complementary to at least about 10, 25, 50, 100, 250 or 500 nucleotides or an entire ORX coding strand, or to only a portion thereof. Nucleic acid molecules encoding fragments, homologs, derivatives and analogs of an ORX protein or antisense nucleic acids complementary to an ORX nucleic acid sequence of GenBank Accession Numbers AF022649, AF073959-073989, AF127814-127907, and AF179716-179843 are additionally provided.

In one embodiment, an antisense nucleic acid molecule is antisense to a "coding region" of the coding strand of a nucleotide sequence encoding ORX. The term "coding region" refers to the region of the nucleotide sequence comprising codons which are translated into amino acid residues. In another embodiment, the antisense nucleic acid molecule is antisense to a "noncoding region" of the coding strand of a nucleotide sequence encoding ORX. The term "noncoding region" refers to 5' and 3' sequences which flank the coding region that are not translated into amino acids (i.e., also referred to as 5' and 3' untranslated regions).

Given the coding strand sequences encoding ORX disclosed herein, antisense nucleic acids of the invention can be designed according to the rules of Watson and Crick or Hoogsteen base pairing. The antisense nucleic acid molecule can be complementary to the entire coding region of ORX mRNA, but more preferably is an oligonucleotide that is antisense to only a

portion of the coding or noncoding region of ORX mRNA. For example, the antisense oligonucleotide can be complementary to the region surrounding the translation start site of ORX mRNA. An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis or enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (e.g., an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, e.g., phosphorothioate derivatives and acridine substituted nucleotides can be used.

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Examples of modified nucleotides that can be used to generate the antisense nucleic acid include: 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine. 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, 15 N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, 20 queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an antisense orientation (i.e., RNA transcribed from the 25 inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest, described further in the following subsection).

The antisense nucleic acid molecules of the invention are typically administered to a subject or generated *in situ* such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding an ORX protein to thereby inhibit expression of the protein, *e.g.*, by inhibiting transcription and/or translation. The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid

molecule that binds to DNA duplexes, through specific interactions in the major groove of the double helix. An example of a route of administration of antisense nucleic acid molecules of the invention includes direct injection at a tissue site. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, antisense molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface, *e.g.*, by linking the antisense nucleic acid molecules to peptides or antibodies that bind to cell surface receptors or antigens. The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of antisense molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

In yet another embodiment, the antisense nucleic acid molecule of the invention is an α-anomeric nucleic acid molecule. An α-anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β-units, the strands run parallel to each other (Gaultier *et al.* (1987) *Nucleic Acids Res* 15: 6625-6641). The antisense nucleic acid molecule can also comprise a 2'-o-methylribonucleotide (Inoue *et al.* (1987) *Nucleic Acids Res* 15: 6131-6148) or a chimeric RNA -DNA analogue (Inoue *et al.* (1987) *FEBS Lett* 215: 327-330).

Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject.

## **ORX Ribozymes and PNA moieties**

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In still another embodiment, an antisense nucleic acid of the invention is a ribozyme. Ribozymes are catalytic RNA molecules with ribonuclease activity that are capable of cleaving a single-stranded nucleic acid, such as a mRNA, to which they have a complementary region. Thus, ribozymes (e.g., hammerhead ribozymes (described in Haselhoff and Gerlach (1988) Nature 334:585-591)) can be used to catalytically cleave ORX mRNA transcripts to thereby inhibit translation of ORX mRNA. A ribozyme having specificity for an ORX-encoding nucleic

acid can be designed based upon the nucleotide sequence of an ORX DNA disclosed herein. For example, a derivative of a Tetrahymena L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in an ORX-encoding mRNA. See, *e.g.*, Cech *et al.* U.S. Pat. No. 4,987,071; and Cech *et al.* U.S. Pat. No. 5,116,742. Alternatively, ORX mRNA can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules. See, *e.g.*, Bartel *et al.*, (1993) *Science* 261:1411-1418.

Alternatively, ORX gene expression can be inhibited by targeting nucleotide sequences complementary to the regulatory region of the ORX (e.g., the ORX promoter and/or enhancers) to form triple helical structures that prevent transcription of the ORX gene in target cells. See generally, Helene. (1991) Anticancer Drug Des. 6: 569-84; Helene. et al. (1992) Ann. N.Y. Acad. Sci. 660:27-36; and Maher (1992) Bioassays 14: 807-15.

In various embodiments, the nucleic acids of ORX can be modified at the base moiety, sugar moiety or phosphate backbone to improve, e.g., the stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acids can be modified to generate peptide nucleic acids (see Hyrup et al. (1996) Bioorg Med Chem 4: 5-23). As used herein, the terms "peptide nucleic acids" or "PNAs" refer to nucleic acid mimics, e.g., DNA mimics, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described in Hyrup et al. (1996) above; Perry-O'Keefe et al. (1996) PNAS 93: 14670-675.

PNAs of ORX can be used in therapeutic and diagnostic applications. For example, PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, e.g., inducing transcription or translation arrest or inhibiting replication. PNAs of ORX can also be used, e.g., in the analysis of single base pair mutations in a gene by, e.g., PNA directed PCR clamping; as artificial restriction enzymes when used in combination with other enzymes, e.g., S1 nucleases (Hyrup B. (1996) above); or as probes or primers for DNA sequence and hybridization (Hyrup et al. (1996), above; Perry-O'Keefe (1996), above).

In another embodiment, PNAs of ORX can be modified, e.g., to enhance their stability or cellular uptake, by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras of ORX can be generated that may combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes, e.g., RNase H and DNA polymerases, to interact with the DNA portion while the PNA portion would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation (Hyrup (1996) above). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup (1996) above and Finn et al. (1996) Nucl Acids Res 24: 3357-63. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry, and modified nucleoside analogs, e.g., 5'-(4-methoxytrityl) amino-5'-deoxy-thymidine phosphoramidite, can be used between the PNA and the 5' end of DNA (Mag et al. (1989) Nucl Acid Res 17: 5973-88). PNA monomers are then coupled in a stepwise manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment (Finn et al. (1996) above). Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment. See, Petersen et al. (1975) Bioorg Med Chem Lett 5: 1119-11124.

In other embodiments, the oligonucleotide may include other appended groups such as peptides (e.g., for targeting host cell receptors in vivo), or agents facilitating transport across the cell membrane (see, e.g., Letsinger et al., 1989, Proc. Natl. Acad. Sci. U.S.A. 86:6553-6556; Lemaitre et al., 1987, Proc. Natl. Acad. Sci. 84:648-652; PCT Publication No. W088/09810) or the blood-brain barrier (see, e.g., PCT Publication No. W089/10134). In addition, oligonucleotides can be modified with hybridization triggered cleavage agents (See, e.g., Krol et al., 1988, BioTechniques 6:958-976) or intercalating agents. (See, e.g., Zon, 1988, Pharm. Res. 5: 539-549). To this end, the oligonucleotide may be conjugated to another molecule, e.g., a peptide, a hybridization triggered cross-linking agent, a transport agent, a hybridization-triggered cleavage agent, etc.

## **ORX Polypeptides**

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An ORX polypeptide of the invention includes the ORX-like protein whose sequence is provided in GenBank Accession Nos. AF127814, AF127816-127819, AF127821-127824, AF127836-127837, AF127840, AF127845-127848, AF127851-127852, AF127857, AF127859, AF127861-127862, AF127865, AF127867-127868, AF127870-127872, AF127874-127884, AF127886, AF127888, AF127896-127904, AF127906-127907, AF179716-179717, AF179720-179728, AF179730-179737, AF179739-179746, AF179748-179750, AF179752, AF179755-179756, AF179758-179761, AF179766-179767, AF179770-179771, AF179773-179775, AF179777-179779, AF179784-179788, AF179790-179792, AF179794, AF179796-179799, AF179802-179811, AF179814, AF179816-179818, AF179820, AF179822-179832, AF179834-179839, AF179841-179843, and AF073959-073989. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue of the ORX polypeptide while still encoding a protein that maintains its ORX-like activities and physiological functions, or a functional fragment thereof. In some embodiments, up to 20% or more of the residues may be so changed in the mutant or variant protein. In some embodiments, the ORX polypeptide according to the invention is a mature polypeptide.

In general, an ORX -like variant that preserves ORX-like function includes any variant in which residues at a particular position in the sequence have been substituted by other amino acids, and further include the possibility of inserting an additional residue or residues between two residues of the parent protein as well as the possibility of deleting one or more residues from the parent sequence. Any amino acid substitution, insertion, or deletion is encompassed by the invention. In favorable circumstances, the substitution is a conservative substitution as defined above.

One aspect of the invention pertains to isolated ORX proteins, and biologically active portions thereof, or derivatives, fragments, analogs or homologs thereof. Also provided are polypeptide fragments suitable for use as immunogens to raise anti-ORX antibodies. In one embodiment, native ORX proteins can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, ORX proteins are produced by recombinant DNA techniques. Alternative to recombinant expression, an ORX protein or polypeptide can be synthesized chemically using standard peptide synthesis techniques.

An "isolated" or "purified" protein or biologically active portion thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the ORX protein is derived, or substantially free from chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of ORX protein in which the protein is separated from cellular components of the cells from which it is isolated or recombinantly produced. In one embodiment, the language "substantially free of cellular material" includes preparations of ORX protein having less than about 30% (by dry weight) of non-ORX protein (also referred to herein as a "contaminating protein"), more preferably less than about 20% of non-ORX protein, still more preferably less than about 10% of non-ORX protein, and most preferably less than about 5% non-ORX protein. When the ORX protein or biologically active portion thereof is recombinantly produced, it is also preferably substantially free of culture medium, *i.e.*, culture medium represents less than about 20%, more preferably less than about 10%, and most preferably less than about 5% of the volume of the protein preparation.

The language "substantially free of chemical precursors or other chemicals" includes preparations of ORX protein in which the protein is separated from chemical precursors or other chemicals that are involved in the synthesis of the protein. In one embodiment, the language "substantially free of chemical precursors or other chemicals" includes preparations of ORX protein having less than about 30% (by dry weight) of chemical precursors or non-ORX chemicals, more preferably less than about 20% chemical precursors or non-ORX chemicals, still more preferably less than about 10% chemical precursors or non-ORX chemicals, and most preferably less than about 5% chemical precursors or non-ORX chemicals.

Biologically active portions of an ORX protein include peptides comprising amino acid sequences sufficiently homologous to or derived from the amino acid sequence of the ORX protein, e.g., the amino acid sequence of the ORX polypeptides that include fewer amino acids than the full length ORX proteins, and exhibit at least one activity of an ORX protein. Typically, biologically active portions comprise a domain or motif with at least one activity of the ORX protein. A biologically active portion of an ORX protein can be a polypeptide which is, for example, 10, 25, 50, 100 or more amino acids in length.

In some embodiments, an ORX protein of the invention includes the amino acid sequence of the herein described polypeptide and a number of amino acids on the amino terminus of the

ORX protein, the carboxy terminus if the ORX protein, or a number of amino acids on both termni of the disclosed ORX protein. Thus, the ORX protein can include 1, 2, 3, 4, 5, 10, 15, 20, 25, 50, or 75 or more amino acids on the amino terminus, the carboxy terminus, or both termini of the disclosed amino acid sequence.

A biologically active portion of an ORX protein of the present invention may contain at least one of the above-identified domains conserved between the ORX proteins, e.g. TSR modules. Moreover, other biologically active portions, in which other regions of the protein are deleted, can be prepared by recombinant techniques and evaluated for one or more of the functional activities of a native ORX protein.

In other embodiments, the ORX protein has an amino acid sequence of an ORX polypeptides. In other embodiments, the ORX protein is substantially homologous to an ORX polypeptide and retains the functional activity of the ORX polypeptide yet differs in amino acid sequence due to natural allelic variation or mutagenesis, as described in detail below. Accordingly, in another embodiment, the ORX protein is a protein that comprises an amino acid sequence at least about 45% homologous to the amino acid sequence of an ORX polypeptide and retains the functional activity of the ORX polypeptides.

#### Determining homology between two or more sequence

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To determine the percent homology of two amino acid sequences or of two nucleic acids, the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in either of the sequences being compared for optimal alignment between the sequences). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are homologous at that position (i.e., as used herein amino acid or nucleic acid "homology" is equivalent to amino acid or nucleic acid "identity").

The nucleic acid sequence homology may be determined as the degree of identity between two sequences. The homology may be determined using computer programs known in the art, such as GAP software provided in the GCG program package. See, *Needleman and Wunsch* 1970 *J Mol Biol* 48: 443-453. Using GCG GAP software with the following settings for nucleic acid sequence comparison: GAP creation penalty of 5.0 and GAP extension penalty of 0.3, the

coding region of the analogous nucleic acid sequences referred to above exhibits a degree of identity preferably of at least 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99%, with the CDS (encoding) part of the DNA sequence shown in GenBank Accession Numbers AF022649, AF073959-073989, AF127814-127907, and AF179716-179843.

The term "sequence identity" refers to the degree to which two polynucleotide or polypeptide sequences are identical on a residue-by-residue basis over a particular region of comparison. The term "percentage of sequence identity" is calculated by comparing two optimally aligned sequences over that region of comparison, determining the number of positions at which the identical nucleic acid base (e.g., A, T, C, G, U, or I, in the case of nucleic acids) occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the region of comparison (i.e., the window size), and multiplying the result by 100 to yield the percentage of sequence identity. The term "substantial identity" as used herein denotes a characteristic of a polynucleotide sequence, wherein the polynucleotide comprises a sequence that has at least 80 percent sequence identity, preferably at least 85 percent identity and often 90 to 95 percent sequence identity, more usually at least 99 percent sequence identity as compared to a reference sequence over a comparison region. The term "percentage of positive residues" is calculated by comparing two optimally aligned sequences over that region of comparison, determining the number of positions at which the identical and conservative amino acid substitutions, as defined above, occur in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the region of comparison (i.e., the window size), and multiplying the result by 100 to yield the percentage of positive residues.

## Chimeric and fusion proteins

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The invention also provides ORX chimeric or fusion proteins. As used herein, an ORX "chimeric protein" or "fusion protein" comprises an ORX polypeptide operatively linked to a non-ORX polypeptide. An "ORX polypeptide" refers to a polypeptide having an amino acid sequence corresponding to ORX, whereas a "non-ORX polypeptide" refers to a polypeptide having an amino acid sequence corresponding to a protein that is not substantially homologous to the ORX protein, e.g., a protein that is different from the ORX protein and that is derived from the same or a different organism. Within an ORX fusion protein the ORX polypeptide can

correspond to all or a portion of an ORX protein. In one embodiment, an ORX fusion protein comprises at least one biologically active portion of an ORX protein. In another embodiment, an ORX fusion protein comprises at least two biologically active portions of an ORX protein. Within the fusion protein, the term "operatively linked" is intended to indicate that the ORX polypeptide and the non-ORX polypeptide are fused in-frame to each other. The non-ORX polypeptide can be fused to the N-terminus or C-terminus of the ORX polypeptide.

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For example, in one embodiment an ORX fusion protein comprises an ORX polypeptide operably linked to the extracellular domain of a second protein. Such fusion proteins can be further utilized in screening assays for compounds that modulate ORX activity (such assays are described in detail below).

In another embodiment, the fusion protein is a GST-ORX fusion protein in which the ORX sequences are fused to the C-terminus of the GST (*i.e.*, glutathione S-transferase) sequences. Such fusion proteins can facilitate the purification of recombinant ORX.

In another embodiment, the fusion protein is an ORX-immunoglobulin fusion protein in which the ORX sequences comprising one or more domains are fused to sequences derived from a member of the immunoglobulin protein family. The ORX-immunoglobulin fusion proteins of the invention can be incorporated into pharmaceutical compositions and administered to a subject to inhibit an interaction between an ORX ligand and an ORX protein on the surface of a cell, to thereby suppress ORX-mediated signal transduction *in vivo*. In one nonlimiting example, a contemplated ORX ligand of the invention is the ORX receptor. The ORX-immunoglobulin fusion proteins can be used to affect the bioavailability of an ORX cognate ligand. Inhibition of the ORX ligand/ORX interaction may be useful therapeutically for both the treatment of proliferative and differentiative disorders, *e,g.*, cancer as well as modulating (*e.g.*, promoting or inhibiting) cell survival. Moreover, the ORX-immunoglobulin fusion proteins of the invention can be used as immunogens to produce anti-ORX antibodies in a subject, to purify ORX ligands, and in screening assays to identify molecules that inhibit the interaction of ORX with an ORX ligand.

An ORX chimeric or fusion protein of the invention can be produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different polypeptide sequences are ligated together in-frame in accordance with conventional techniques, e.g., by employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion

to provide for appropriate termini, filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and enzymatic ligation. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers that give rise to complementary overhangs between two consecutive gene fragments that can subsequently be annealed and reamplified to generate a chimeric gene sequence (see, for example, Ausubel et al. (eds.) CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (e.g., a GST polypeptide). An ORX-encoding nucleic acid can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the ORX protein.

## **ORX** agonists and antagonists

The present invention also pertains to variants of the ORX proteins that function as either ORX agonists (mimetics) or as ORX antagonists. Variants of the ORX protein can be generated by mutagenesis, e.g., discrete point mutation or truncation of the ORX protein. An agonist of the ORX protein can retain substantially the same, or a subset of, the biological activities of the naturally occurring form of the ORX protein. An antagonist of the ORX protein can inhibit one or more of the activities of the naturally occurring form of the ORX protein by, for example, competitively binding to a downstream or upstream member of a cellular signaling cascade which includes the ORX protein. Thus, specific biological effects can be elicited by treatment with a variant of limited function. In one embodiment, treatment of a subject with a variant having a subset of the biological activities of the naturally occurring form of the protein has fewer side effects in a subject relative to treatment with the naturally occurring form of the ORX proteins.

Variants of the ORX protein that function as either ORX agonists (mimetics) or as ORX antagonists can be identified by screening combinatorial libraries of mutants, e.g., truncation mutants, of the ORX protein for ORX protein agonist or antagonist activity. In one embodiment, a variegated library of ORX variants is generated by combinatorial mutagenesis at the nucleic acid level and is encoded by a variegated gene library. A variegated library of ORX variants can be produced by, for example, enzymatically ligating a mixture of synthetic oligonucleotides into

gene sequences such that a degenerate set of potential ORX sequences is expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (e.g., for phage display) containing the set of ORX sequences therein. There are a variety of methods which can be used to produce libraries of potential ORX variants from a degenerate oligonucleotide sequence.

Chemical synthesis of a degenerate gene sequence can be performed in an automatic DNA synthesizer, and the synthetic gene then ligated into an appropriate expression vector. Use of a degenerate set of genes allows for the provision, in one mixture, of all of the sequences encoding the desired set of potential ORX sequences. Methods for synthesizing degenerate oligonucleotides are known in the art (see, e.g., Narang (1983) Tetrahedron 39:3; Itakura et al. (1984) Annu Rev Biochem 53:323; Itakura et al. (1984) Science 198:1056; Ike et al. (1983) Nucl Acid Res 11:477.

# Polypeptide libraries

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In addition, libraries of fragments of the ORX protein coding sequence can be used to generate a variegated population of ORX fragments for screening and subsequent selection of variants of an ORX protein. In one embodiment, a library of coding sequence fragments can be generated by treating a double stranded PCR fragment of an ORX coding sequence with a nuclease under conditions wherein nicking occurs only about once per molecule, denaturing the double stranded DNA, renaturing the DNA to form double stranded DNA that can include sense/antisense pairs from different nicked products, removing single stranded portions from reformed duplexes by treatment with S1 nuclease, and ligating the resulting fragment library into an expression vector. By this method, an expression library can be derived which encodes N-terminal and internal fragments of various sizes of the ORX protein.

Several techniques are known in the art for screening gene products of combinatorial libraries made by point mutations or truncation, and for screening cDNA libraries for gene products having a selected property. Such techniques are adaptable for rapid screening of the gene libraries generated by the combinatorial mutagenesis of ORX proteins. The most widely used techniques, which are amenable to high throughput analysis, for screening large gene libraries typically include cloning the gene library into replicable expression vectors, transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates isolation

of the vector encoding the gene whose product was detected. Recrusive ensemble mutagenesis (REM), a new technique that enhances the frequency of functional mutants in the libraries, can be used in combination with the screening assays to identify ORX variants (Arkin and Yourvan (1992) PNAS 89:7811-7815; Delgrave *et al.* (1993) Protein Engineering 6:327-331).

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#### **ORX Antibodies**

Also included in the invention are antibodies to ORX proteins, or fragments of ORX proteins. The term "antibody" as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin (Ig) molecules, *i.e.*, molecules that contain an antigen binding site that specifically binds (immunoreacts with) an antigen. Such antibodies include, but are not limited to, polyclonal, monoclonal, chimeric, single chain,  $F_{ab}$ ,  $F_{ab}$  and  $F_{(ab)2}$  fragments, and an  $F_{ab}$  expression library. In general, an antibody molecule obtained from humans relates to any of the classes IgG, IgM, IgA, IgE and IgD, which differ from one another by the nature of the heavy chain present in the molecule. Certain classes have subclasses as well, such as  $IgG_1$ ,  $IgG_2$ , and others. Furthermore, in humans, the light chain may be a kappa chain or a lambda chain. Reference herein to antibodies includes a reference to all such classes, subclasses and types of human antibody species.

An isolated ORX-related protein of the invention may be intended to serve as an antigen, or a portion or fragment thereof, and additionally can be used as an immunogen to generate antibodies that immunospecifically bind the antigen, using standard techniques for polyclonal and monoclonal antibody preparation. The full-length protein can be used or, alternatively, the invention provides antigenic peptide fragments of the antigen for use as immunogens. An antigenic peptide fragment comprises at least 6 amino acid residues of the amino acid sequence of the full length protein and encompasses an epitope thereof such that an antibody raised against the peptide forms a specific immune complex with the full length protein or with any fragment that contains the epitope. Preferably, the antigenic peptide comprises at least 10 amino acid residues, or at least 15 amino acid residues, or at least 20 amino acid residues, or at least 30 amino acid residues. Preferred epitopes encompassed by the antigenic peptide are regions of the protein that are located on its surface; commonly these are hydrophilic regions.

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In certain embodiments of the invention, at least one epitope encompassed by the antigenic peptide is a region of ORX-related protein that is located on the surface of the protein,

e.g., a hydrophilic region. A hydrophobicity analysis of the human ORX-related protein sequence will indicate which regions of an ORX-related protein are particularly hydrophilic and, therefore, are likely to encode surface residues useful for targeting antibody production. As a means for targeting antibody production, hydropathy plots showing regions of hydrophilicity and hydrophobicity may be generated by any method well known in the art, including, for example, the Kyte Doolittle or the Hopp Woods methods, either with or without Fourier transformation. See, e.g., Hopp and Woods, 1981, Proc. Nat. Acad. Sci. USA 78: 3824-3828; Kyte and Doolittle 1982, J. Mol. Biol. 157: 105-142, each of which is incorporated herein by reference in its entirety. Antibodies that are specific for one or more domains within an antigenic protein, or derivatives, fragments, analogs or homologs thereof, are also provided herein.

A protein of the invention, or a derivative, fragment, analog, homolog or ortholog thereof, may be utilized as an immunogen in the generation of antibodies that immunospecifically bind these protein components.

Various procedures known within the art may be used for the production of polyclonal or monoclonal antibodies directed against a protein of the invention, or against derivatives, fragments, analogs homologs or orthologs thereof (see, for example, Antibodies: A Laboratory Manual, Harlow E, and Lane D, 1988, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, incorporated herein by reference). Some of these antibodies are discussed below.

#### 20 Polyclonal Antibodies

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For the production of polyclonal antibodies, various suitable host animals (e.g., rabbit, goat, mouse or other mammal) may be immunized by one or more injections with the native protein, a synthetic variant thereof, or a derivative of the foregoing. An appropriate immunogenic preparation can contain, for example, the naturally occurring immunogenic protein, a chemically synthesized polypeptide representing the immunogenic protein, or a recombinantly expressed immunogenic protein. Furthermore, the protein may be conjugated to a second protein known to be immunogenic in the mammal being immunized. Examples of such immunogenic proteins include but are not limited to keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. The preparation can further include an adjuvant. Various adjuvants used to increase the immunological response include, but are not limited to, Freund's (complete and incomplete), mineral gels (e.g., aluminum hydroxide), surface

active substances (e.g., lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, dinitrophenol, etc.), adjuvants usable in humans such as Bacille Calmette-Guerin and Corynebacterium parvum, or similar immunostimulatory agents. Additional examples of adjuvants which can be employed include MPL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate).

The polyclonal antibody molecules directed against the immunogenic protein can be isolated from the mammal (e.g., from the blood) and further purified by well known techniques, such as affinity chromatography using protein A or protein G, which provide primarily the IgG fraction of immune serum. Subsequently, or alternatively, the specific antigen which is the target of the immunoglobulin sought, or an epitope thereof, may be immobilized on a column to purify the immune specific antibody by immunoaffinity chromatography. Purification of immunoglobulins is discussed, for example, by D. Wilkinson (The Scientist, published by The Scientist, Inc., Philadelphia PA, Vol. 14, No. 8 (April 17, 2000), pp. 25-28).

## **Monoclonal Antibodies**

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The term "monoclonal antibody" (MAb) or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one molecular species of antibody molecule consisting of a unique light chain gene product and a unique heavy chain gene product. In particular, the complementarity determining regions (CDRs) of the monoclonal antibody are identical in all the molecules of the population. MAbs thus contain an antigen binding site capable of immunoreacting with a particular epitope of the antigen characterized by a unique binding affinity for it.

Monoclonal antibodies can be prepared using hybridoma methods, such as those described by Kohler and Milstein, <u>Nature</u>, <u>256</u>:495 (1975). In a hybridoma method, a mouse, hamster, or other appropriate host animal, is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes can be immunized *in vitro*.

The immunizing agent will typically include the protein antigen, a fragment thereof or a fusion protein thereof. Generally, either peripheral blood lymphocytes are used if cells of human origin are desired, or spleen cells or lymph node cells are used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable

fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, Monoclonal Antibodies: Principles and Practice, Academic Press, (1986) pp. 59-103). Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine and human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells can be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine ("HAT medium"), which substances prevent the growth of HGPRT-deficient cells.

Preferred immortalized cell lines are those that fuse efficiently, support stable high level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk Institute Cell Distribution Center, San Diego, California and the American Type Culture Collection, Manassas, Virginia. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies (Kozbor, J. Immunol., 133:3001 (1984); Brodeur et al., Monoclonal Antibody Production Techniques and Applications, Marcel Dekker, Inc., New York, (1987) pp. 51-63).

The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against the antigen. Preferably, the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). Such techniques and assays are known in the art. The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson and Pollard, <u>Anal. Biochem.</u>, <u>107</u>:220 (1980). Preferably, antibodies having a high degree of specificity and a high binding affinity for the target antigen are isolated.

After the desired hybridoma cells are identified, the clones can be subcloned by limiting dilution procedures and grown by standard methods. Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells can be grown *in vivo* as ascites in a mammal.

The monoclonal antibodies secreted by the subclones can be isolated or purified from the culture medium or ascites fluid by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

The monoclonal antibodies can also be made by recombinant DNA methods, such as those described in U.S. Patent No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA can be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also can be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences (U.S. Patent No. 4,816,567; Morrison, Nature 368, 812-13 (1994)) or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the invention, or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody.

#### **Humanized Antibodies**

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The antibodies directed against the protein antigens of the invention can further comprise humanized antibodies or human antibodies. These antibodies are suitable for administration to humans without engendering an immune response by the human against the administered immunoglobulin. Humanized forms of antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')<sub>2</sub> or other antigenbinding subsequences of antibodies) that are principally comprised of the sequence of a human immunoglobulin, and contain minimal sequence derived from a non-human immunoglobulin. Humanization can be performed following the method of Winter and co-workers (Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-327 (1988); Verhoeyen et al.,

Science, 239:1534-1536 (1988)), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. (See also U.S. Patent No. 5,225,539.) In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies can also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the framework regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin (Jones et al., 1986; Riechmann et al., 1988; and Presta, Curr. Op. Struct. Biol., 2:593-596 (1992)).

# **Human Antibodies**

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Fully human antibodies relate to antibody molecules in which essentially the entire sequences of both the light chain and the heavy chain, including the CDRs, arise from human genes. Such antibodies are termed "human antibodies", or "fully human antibodies" herein. Human monoclonal antibodies can be prepared by the trioma technique; the human B-cell hybridoma technique (see Kozbor, et al., 1983 Immunol Today 4: 72) and the EBV hybridoma technique to produce human monoclonal antibodies (see Cole, et al., 1985 In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96). Human monoclonal antibodies may be utilized in the practice of the present invention and may be produced by using human hybridomas (see Cote, et al., 1983. Proc Natl Acad Sci USA 80: 2026-2030) or by transforming human B-cells with Epstein Barr Virus *in vitro* (see Cole, et al., 1985 In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96).

In addition, human antibodies can also be produced using additional techniques, including phage display libraries (Hoogenboom and Winter, <u>J. Mol. Biol., 227</u>:381 (1991); Marks et al., <u>J. Mol. Biol., 222</u>:581 (1991)). Similarly, human antibodies can be made by introducing human immunoglobulin loci into transgenic animals, *e.g.*, mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon

challange human antihody production is charged which alocaly recombles that soon in human

in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, for example, in U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, and in Marks et al. (Bio/Technology 10, 779-783 (1992)); Lonberg et al. (Nature 368 856-859 (1994)); Morrison (Nature 368, 812-13 (1994)); Fishwild et al., (Nature Biotechnology 14, 845-51 (1996)); Neuberger (Nature Biotechnology 14, 826 (1996)); and Lonberg and Huszar (Intern. Rev. Immunol. 13 65-93 (1995)).

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Human antibodies may additionally be produced using transgenic nonhuman animals which are modified so as to produce fully human antibodies rather than the animal's endogenous antibodies in response to challenge by an antigen. (See PCT publication WO94/02602). The endogenous genes encoding the heavy and light immunoglobulin chains in the nonhuman host have been incapacitated, and active loci encoding human heavy and light chain immunoglobulins are inserted into the host's genome. The human genes are incorporated, for example, using yeast artificial chromosomes containing the requisite human DNA segments. An animal which provides all the desired modifications is then obtained as progeny by crossbreeding intermediate transgenic animals containing fewer than the full complement of the modifications. The preferred embodiment of such a nonhuman animal is a mouse, and is termed the Xenomouse<sup>TM</sup> as disclosed in PCT publications WO 96/33735 and WO 96/34096. This animal produces B cells which secrete fully human immunoglobulins. The antibodies can be obtained directly from the animal after immunization with an immunogen of interest, as, for example, a preparation of a polyclonal antibody, or alternatively from immortalized B cells derived from the animal, such as hybridomas producing monoclonal antibodies. Additionally, the genes encoding the immunoglobulins with human variable regions can be recovered and expressed to obtain the antibodies directly, or can be further modified to obtain analogs of antibodies such as, for example, single chain Fv molecules.

An example of a method of producing a nonhuman host, exemplified as a mouse, lacking expression of an endogenous immunoglobulin heavy chain is disclosed in U.S. Patent No. 5,939,598. It can be obtained by a method including deleting the J segment genes from at least one endogenous heavy chain locus in an embryonic stem cell to prevent rearrangement of the locus and to prevent formation of a transcript of a rearranged immunoglobulin heavy chain locus, the deletion being effected by a targeting vector containing a gene encoding a selectable marker;

and producing from the embryonic stem cell a transgenic mouse whose somatic and germ cells contain the gene encoding the selectable marker.

A method for producing an antibody of interest, such as a human antibody, is disclosed in U.S. Patent No. 5,916,771. It includes introducing an expression vector that contains a nucleotide sequence encoding a heavy chain into one mammalian host cell in culture, introducing an expression vector containing a nucleotide sequence encoding a light chain into another mammalian host cell, and fusing the two cells to form a hybrid cell. The hybrid cell expresses an antibody containing the heavy chain and the light chain.

In a further improvement on this procedure, a method for identifying a clinically relevant epitope on an immunogen, and a correlative method for selecting an antibody that binds immunospecifically to the relevant epitope with high affinity, are disclosed in PCT publication WO 99/53049.

# Fab Fragments and Single Chain Antibodies

According to the invention, techniques can be adapted for the production of single-chain antibodies specific to an antigenic protein of the invention (see *e.g.*, U.S. Patent No. 4,946,778). In addition, methods can be adapted for the construction of  $F_{ab}$  expression libraries (see *e.g.*, Huse, et al., 1989 Science 246: 1275-1281) to allow rapid and effective identification of monoclonal  $F_{ab}$  fragments with the desired specificity for a protein or derivatives, fragments, analogs or homologs thereof. Antibody fragments that contain the idiotypes to a protein antigen may be produced by techniques known in the art including, but not limited to: (i) an  $F_{(ab)}$  fragment produced by pepsin digestion of an antibody molecule; (ii) an  $F_{ab}$  fragment generated by reducing the disulfide bridges of an  $F_{(ab)}$  fragment; (iii) an  $F_{ab}$  fragment generated by the treatment of the antibody molecule with papain and a reducing agent and (iv)  $F_v$  fragments.

#### **Bispecific Antibodies**

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Bispecific antibodies are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for an antigenic protein of the invention. The second binding target is any other antigen, and advantageously is a cell-surface protein or receptor or receptor subunit.

Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy-chain/light-chain pairs, where the two heavy chains have different specificities (Milstein and Cuello, Nature, 305:537-539 (1983)). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of ten different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule is usually accomplished by affinity chromatography steps. Similar procedures are disclosed in WO 93/08829, published 13 May 1993, and in Traunecker *et al.*, 1991 *EMBO J.*, 10:3655-3659.

Antibody variable domains with the desired binding specificities (antibody-antigen combining sites) can be fused to immunoglobulin constant domain sequences. The fusion preferably is with an immunoglobulin heavy-chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light-chain binding present in at least one of the fusions. DNAs encoding the immunoglobulin heavy-chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. For further details of generating bispecific antibodies see, for example, Suresh et al., Methods in Enzymology, 121:210 (1986).

According to another approach described in WO 96/27011, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface comprises at least a part of the CH3 region of an antibody constant domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (e.g. tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (e.g. alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

Bispecific antibodies can be prepared as full length antibodies or antibody fragments (e.g. F(ab')<sub>2</sub> bispecific antibodies). Techniques for generating bispecific antibodies from antibody fragments have been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. Brennan et al., Science 229:81 (1985) describe a procedure

wherein intact antibodies are proteolytically cleaved to generate F(ab')<sub>2</sub> fragments. These fragments are reduced in the presence of the dithiol complexing agent sodium arsenite to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

Additionally, Fab' fragments can be directly recovered from E. coli and chemically coupled to form bispecific antibodies. Shalaby et al., J. Exp. Med. 175:217-225 (1992) describe the production of a fully humanized bispecific antibody F(ab')<sub>2</sub> molecule. Each Fab' fragment was separately secreted from E. coli and subjected to directed chemical coupling *in vitro* to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T cells, as well as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets.

Various techniques for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny et al., J. Immunol. 148(5):1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers. The "diabody" technology described by Hollinger et al., Proc. Natl. Acad. Sci. USA 90:6444-6448 (1993) has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a heavy-chain variable domain (V<sub>H</sub>) connected to a light-chain variable domain (V<sub>L</sub>) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the V<sub>H</sub> and V<sub>L</sub> domains of one fragment are forced to pair with the complementary V<sub>L</sub> and V<sub>H</sub> domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See, Gruber et al., J. Immunol. 152:5368 (1994).

Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared. Tutt et al., <u>J. Immunol.</u> 147:60 (1991).

Exemplary bispecific antibodies can bind to two different epitopes, at least one of which originates in the protein antigen of the invention. Alternatively, an anti-antigenic arm of an immunoglobulin molecule can be combined with an arm which binds to a triggering molecule on a leukocyte such as a T-cell receptor molecule (e.g. CD2, CD3, CD28, or B7), or Fc receptors for IgG (Fc?R), such as Fc?RI (CD64), Fc?RII (CD32) and Fc?RII (CD16) so as to focus cellular defense mechanisms to the cell expressing the particular antigen. Bispecific antibodies can also be used to direct cytotoxic agents to cells which express a particular antigen. These antibodies possess an antigen-binding arm and an arm which binds a cytotoxic agent or a radionuclide chelator, such as EOTUBE, DPTA, DOTA, or TETA. Another bispecific antibody of interest binds the protein antigen described herein and further binds tissue factor (TF).

## **Heteroconjugate Antibodies**

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Heteroconjugate antibodies are also within the scope of the present invention. Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells (U.S. Patent No. 4,676,980), and for treatment of HIV infection (WO 91/00360; WO 92/200373; EP 03089). It is contemplated that the antibodies can be prepared *in vitro* using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins can be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptobutyrimidate and those disclosed, for example, in U.S. Patent No. 4,676,980.

#### **Effector Function Engineering**

It can be desirable to modify the antibody of the invention with respect to effector function, so as to enhance, *e.g.*, the effectiveness of the antibody in treating cancer. For example, cysteine residue(s) can be introduced into the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated can have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). See Caron et al., J. Exp Med., 176: 1191-1195 (1992) and Shopes, J. Immunol., 148: 2918-2922 (1992). Homodimeric antibodies with enhanced antitumor activity can also be prepared using heterobifunctional cross-linkers as described in Wolff et al. Cancer Research, 53: 2560-2565 (1993). Alternatively, an antibody can be engineered that has dual Fc regions and can thereby have enhanced complement lysis and ADCC capabilities. See Stevenson et al., Anti-Cancer Drug Design, 3: 219-230 (1989).

#### **Immunoconjugates**

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The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a chemotherapeutic agent, toxin (e.g., an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (i.e., a radioconjugate).

Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above. Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from Pseudomonas aeruginosa), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, Aleurites fordii proteins, dianthin proteins, Phytolaca americana proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies. Examples include  $^{212}$ Bi,  $^{131}$ I,  $^{131}$ In,  $^{90}$ Y, and  $^{186}$ Re.

Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutareldehyde), bis-azido

compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et al., Science, 238: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026.

In another embodiment, the antibody can be conjugated to a "receptor" (such streptavidin) for utilization in tumor pretargeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then administration of a "ligand" (e.g., avidin) that is in turn conjugated to a cytotoxic agent.

## **ORX Recombinant Expression Vectors and Host Cells**

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Another aspect of the invention pertains to vectors, preferably expression vectors, containing a nucleic acid encoding an ORX protein, or derivatives, fragments, analogs or homologs thereof. As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively-linked. Such vectors are referred to herein as "expression vectors". In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" can be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors

(e.g., replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The recombinant expression vectors of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell, which means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, that is operatively-linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably-linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner that allows for expression of the nucleotide sequence (e.g., in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell).

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The term "regulatory sequence" is intended to includes promoters, enhancers and other expression control elements (e.g., polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990). Regulatory sequences include those that direct constitutive expression of a nucleotide sequence in many types of host cell and those that direct expression of the nucleotide sequence only in certain host cells (e.g., tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, etc. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein (e.g., ORX proteins, mutant forms of ORX proteins, fusion proteins, etc.).

The recombinant expression vectors of the invention can be designed for expression of ORX proteins in prokaryotic or eukaryotic cells. For example, ORX proteins can be expressed in bacterial cells such as *Escherichia coli*, insect cells (using baculovirus expression vectors) yeast cells or mammalian cells. Suitable host cells are discussed further in Goeddel, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990). Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

Expression of proteins in prokaryotes is most often carried out in *Escherichia coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or

non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: (i) to increase expression of recombinant protein; (ii) to increase the solubility of the recombinant protein; and (iii) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith and Johnson, 1988. Gene 67: 31-40), pMAL (New England Biolabs, Beverly, Mass.) and pRIT5 (Pharmacia, Piscataway, N.J.) that fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein.

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Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amrann *et al.*, (1988) *Gene* 69:301-315) and pET 11d (Studier *et al.*, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990) 60-89).

One strategy to maximize recombinant protein expression in *E. coli* is to express the protein in a host bacteria with an impaired capacity to proteolytically cleave the recombinant protein. *See, e.g.*, Gottesman, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990) 119-128. Another strategy is to alter the nucleic acid sequence of the nucleic acid to be inserted into an expression vector so that the individual codons for each amino acid are those preferentially utilized in *E. coli* (see, e.g., Wada, et al., 1992. Nucl. Acids Res. 20: 2111-2118). Such alteration of nucleic acid sequences of the invention can be carried out by standard DNA synthesis techniques.

In another embodiment, the ORX expression vector is a yeast expression vector. Examples of vectors for expression in yeast *Saccharomyces cerivisae* include pYepSec1 (Baldari, et al., 1987. EMBO J. 6: 229-234), pMFa (Kurjan and Herskowitz, 1982. Cell 30: 933-943), pJRY88 (Schultz et al., 1987. Gene 54: 113-123), pYES2 (Invitrogen Corporation, San Diego, Calif.), and picZ (InVitrogen Corp, San Diego, Calif.).

Alternatively, ORX can be expressed in insect cells using baculovirus expression vectors. Baculovirus vectors available for expression of proteins in cultured insect cells (e.g., SF9 cells)

include the pAc series (Smith, et al., 1983. Mol. Cell. Biol. 3: 2156-2165) and the pVL series (Lucklow and Summers, 1989. Virology 170: 31-39).

In yet another embodiment, a nucleic acid of the invention is expressed in mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include pCDM8 (Seed, 1987. *Nature* 329: 840) and pMT2PC (Kaufman, *et al.*, 1987. *EMBO J.* 6: 187-195). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, adenovirus 2, cytomegalovirus, and simian virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells see, *e.g.*, Chapters 16 and 17 of Sambrook, *et al.*, MOLECULAR CLONING: A LABORATORY MANUAL. 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989.

In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (e.g., tissue-specific regulatory elements are used to express the nucleic acid). Tissue-specific regulatory elements are known in the art. Non-limiting examples of suitable tissue-specific promoters include the albumin promoter (liver-specific; Pinkert, et al., 1987. Genes Dev. 1: 268-277), lymphoid-specific promoters (Calame and Eaton, 1988. Adv. Immunol. 43: 235-275), in particular promoters of T cell receptors (Winoto and Baltimore, 1989. EMBO J. 8: 729-733) and immunoglobulins (Banerji, et al., 1983. Cell 33: 729-740; Queen and Baltimore, 1983. Cell 33: 741-748), neuron-specific promoters (e.g., the neurofilament promoter; Byrne and Ruddle, 1989. Proc. Natl. Acad. Sci. USA 86: 5473-5477), pancreas-specific promoters (Edlund, et al., 1985. Science 230: 912-916), and mammary gland-specific promoters (e.g., milk whey promoter; U.S. Pat. No. 4,873,316 and European Application Publication No. 264,166). Developmentally-regulated promoters are also encompassed, e.g., the murine hox promoters (Kessel and Gruss, 1990. Science 249: 374-379) and the α-fetoprotein promoter (Campes and Tilghman, 1989. Genes Dev. 3: 537-546).

The invention further provides a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an antisense orientation. That is, the DNA molecule is operatively-linked to a regulatory sequence in a manner that allows for expression (by transcription of the DNA molecule) of an RNA molecule that is antisense to ORX mRNA. Regulatory sequences operatively linked to a nucleic acid cloned in the antisense

orientation can be chosen that direct the continuous expression of the antisense RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen that direct constitutive, tissue specific or cell type specific expression of antisense RNA. The antisense expression vector can be in the form of a recombinant plasmid, phagemid or attenuated virus in which antisense nucleic acids are produced under the control of a high efficiency regulatory region, the activity of which can be determined by the cell type into which the vector is introduced. For a discussion of the regulation of gene expression using antisense genes *see*, *e.g.*, Weintraub, *et al.*, "Antisense RNA as a molecular tool for genetic analysis," *Reviews-Trends in Genetics*, Vol. 1(1) 1986.

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Another aspect of the invention pertains to host cells into which a recombinant expression vector of the invention has been introduced. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but also to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

A host cell can be any prokaryotic or eukaryotic cell. For example, ORX protein can be expressed in bacterial cells such as *E. coli*, insect cells, yeast or mammalian cells (such as human, Chinese hamster ovary cells (CHO) or COS cells). Other suitable host cells are known to those skilled in the art.

Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid (e.g., DNA) into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, et al. (MOLECULAR CLONING: A LABORATORY MANUAL. 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989), and other laboratory manuals.

For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that

encodes a selectable marker (e.g., resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Various selectable markers include those that confer resistance to drugs, such as G418, hygromycin and methotrexate. Nucleic acid encoding a selectable marker can be introduced into a host cell on the same vector as that encoding ORX or can be introduced on a separate vector. Cells stably transfected with the introduced nucleic acid can be identified by drug selection (e.g., cells that have incorporated the selectable marker gene will survive, while the other cells die).

A host cell of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce (*i.e.*, express) ORX protein. Accordingly, the invention further provides methods for producing ORX protein using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of invention (into which a recombinant expression vector encoding ORX protein has been introduced) in a suitable medium such that ORX protein is produced. In another embodiment, the method further comprises isolating ORX protein from the medium or the host cell.

# **Transgenic ORX Animals**

The host cells of the invention can also be used to produce non-human transgenic animals. For example, in one embodiment, a host cell of the invention is a fertilized oocyte or an embryonic stem cell into which ORX protein-coding sequences have been introduced. Such host cells can then be used to create non-human transgenic animals in which exogenous ORX sequences have been introduced into their genome or homologous recombinant animals in which endogenous ORX sequences have been altered. Such animals are useful for studying the function and/or activity of ORX protein and for identifying and/or evaluating modulators of ORX protein activity. As used herein, a "transgenic animal" is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, amphibians, etc. A transgene is exogenous DNA that is integrated into the genome of a cell from which a transgenic animal develops and that remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, a "homologous recombinant animal" is a non-human animal, preferably a mammal, more

preferably a mouse, in which an endogenous ORX gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, e.g., an embryonic cell of the animal, prior to development of the animal.

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A transgenic animal of the invention can be created by introducing ORX-encoding nucleic acid into the male pronuclei of a fertilized oocyte (e.g., by microinjection, retroviral infection) and allowing the oocyte to develop in a pseudopregnant female foster animal. Sequences including GenBank Accession Numbers AF022649, AF073959-073989, AF127814-127907, and AF179716-179843 can be introduced as a transgene into the genome of a non-human animal. Alternatively, a non-human homologue of the human ORX gene, such as a mouse ORX gene, can be isolated based on hybridization to the human ORX cDNA (described further supra) and used as a transgene. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably-linked to the ORX transgene to direct expression of ORX protein to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866; 4,870,009; and 4,873,191; and Hogan, 1986. In: MANIPULATING THE MOUSE EMBRYO, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of the ORX transgene in its genome and/or expression of ORX mRNA in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying a transgene-encoding ORX protein can further be bred to other transgenic animals carrying other transgenes.

To create a homologous recombinant animal, a vector is prepared which contains at least a portion of an ORX gene into which a deletion, addition or substitution has been introduced to thereby alter, e.g., functionally disrupt, the ORX gene. The ORX gene can be a human gene, but more preferably, is a non-human homologue of a human ORX gene. For example, a mouse homologue of human ORX gene of GenBank Accession Numbers AF022649, AF073959-073989, AF127814-127907, and AF179716-179843, can be used to construct a homologous recombination vector suitable for altering an endogenous ORX gene in the mouse genome. In one embodiment, the vector is designed such that, upon homologous recombination, the

endogenous ORX gene is functionally disrupted (i.e., no longer encodes a functional protein; also referred to as a "knock out" vector).

Alternatively, the vector can be designed such that, upon homologous recombination, the endogenous ORX gene is mutated or otherwise altered but still encodes functional protein (e.g., the upstream regulatory region can be altered to thereby alter the expression of the endogenous ORX protein). In the homologous recombination vector, the altered portion of the ORX gene is flanked at its 5'- and 3'-termini by additional nucleic acid of the ORX gene to allow for homologous recombination to occur between the exogenous ORX gene carried by the vector and an endogenous ORX gene in an embryonic stem cell. The additional flanking ORX nucleic acid is of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5'- and 3'-termini) are included in the vector. See, e.g., Thomas, et al., 1987. Cell 51: 503 for a description of homologous recombination vectors. The vector is ten introduced into an embryonic stem cell line (e.g., by electroporation) and cells in which the introduced ORX gene has homologously-recombined with the endogenous ORX gene are selected. See, e.g., Li, et al., 1992. Cell 69: 915.

The selected cells are then injected into a blastocyst of an animal (e.g., a mouse) to form aggregation chimeras. See, e.g., Bradley, 1987. In: TERATOCARCINOMAS AND EMBRYONIC STEM CELLS: A PRACTICAL APPROACH, Robertson, ed. IRL, Oxford, pp. 113-152. A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term. Progeny harboring the homologously-recombined DNA in their germ cells can be used to breed animals in which all cells of the animal contain the homologously-recombined DNA by germline transmission of the transgene. Methods for constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley, 1991. Curr. Opin. Biotechnol. 2: 823-829; PCT International Publication Nos.: WO 90/11354; WO 91/01140; WO 92/0968; and WO 93/04169.

In another embodiment, transgenic non-humans animals can be produced that contain selected systems that allow for regulated expression of the transgene. One example of such a system is the cre/loxP recombinase system of bacteriophage P1. For a description of the cre/loxP recombinase system, See, e.g., Lakso, et al., 1992. Proc. Natl. Acad. Sci. USA 89: 6232-6236.

Another example of a recombinase system is the FLP recombinase system of Saccharomyces cerevisiae. See, O'Gorman, et al., 1991. Science 251:1351-1355. If a cre/loxP recombinase

system is used to regulate expression of the transgene, animals containing transgenes encoding both the Cre recombinase and a selected protein are required. Such animals can be provided through the construction of "double" transgenic animals, e.g., by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase.

Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut,  $et\ al.$ , 1997. Nature 385: 810-813. In brief, a cell (e.g., a somatic cell) from the transgenic animal can be isolated and induced to exit the growth cycle and enter  $G_0$  phase. The quiescent cell can then be fused, e.g., through the use of electrical pulses, to an enucleated oocyte from an animal of the same species from which the quiescent cell is isolated. The reconstructed oocyte is then cultured such that it develops to morula or blastocyte and then transferred to pseudopregnant female foster animal. The offspring borne of this female foster animal will be a clone of the animal from which the cell (e.g., the somatic cell) is isolated.

## **Pharmaceutical Compositions**

The ORX nucleic acid molecules, ORX proteins, and anti-ORX antibodies (also referred to herein as "active compounds") of the invention, and derivatives, fragments, analogs and homologs thereof, can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically comprise the nucleic acid molecule, protein, or antibody and a pharmaceutically acceptable carrier. As used herein, "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. Suitable carriers are described in the most recent edition of Remington's Pharmaceutical Sciences, a standard reference text in the field, which is incorporated herein by reference. Preferred examples of such carriers or diluents include, but are not limited to, water, saline, finger's solutions, dextrose solution, and 5% human serum albumin. Liposomes and non-aqueous vehicles such as fixed oils may also be used. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use

thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

The antibodies disclosed herein can also be formulated as immunoliposomes. Liposomes containing the antibody are prepared by methods known in the art, such as described in Epstein et al., Proc. Natl. Acad. Sci. USA, 82: 3688 (1985); Hwang et al., Proc. Natl. Acad. Sci. USA, 77: 4030 (1980); and U.S. Pat. Nos. 4,485,045 and 4,544,545. Liposomes with enhanced circulation time are disclosed in U.S. Patent No. 5,013,556.

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Particularly useful liposomes can be generated by the reverse-phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol, and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of the antibody of the present invention can be conjugated to the liposomes as described in Martin et al., J. Biol. Chem., 257: 286-288 (1982) via a disulfide-interchange reaction. A chemotherapeutic agent (such as Doxorubicin) is optionally contained within the liposome. See Gabizon et al., J. National Cancer Inst., 81(19): 1484 (1989).

A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (i.e., topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include

physiological saline, bacteriostatic water, Cremophor EL<sup>™</sup> (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound (e.g., an ORX protein or anti-ORX antibody) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the

like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

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For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

The compounds can also be prepared in the form of suppositories (e.g., with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

The nucleic acid molecules of the invention can be inserted into vectors and used as gene therapy vectors. Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (see, e.g., U.S. Patent No. 5,328,470) or by stereotactic injection (see, e.g., Chen, et al., 1994. Proc. Natl. Acad. Sci. USA 91: 3054-3057). The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, e.g., retroviral vectors, the pharmaceutical preparation can include one or more cells that produce the gene delivery system.

Antibodies specifically binding a protein of the invention, as well as other molecules identified by the screening assays disclosed herein, can be administered for the treatment of various disorders in the form of pharmaceutical compositions. Principles and considerations involved in preparing such compositions, as well as guidance in the choice of components are provided, for example, in Remington: The Science And Practice Of Pharmacy 19th ed. (Alfonso R. Gennaro, et al., editors) Mack Pub. Co., Easton, Pa.: 1995; Drug Absorption Enhancement: Concepts, Possibilities, Limitations, And Trends, Harwood Academic Publishers, Langhorne, Pa., 1994; and Peptide And Protein Drug Delivery (Advances In Parenteral Sciences, Vol. 4), 1991, M. Dekker, New York. If the antigenic protein is intracellular and whole antibodies are used as inhibitors, internalizing antibodies are preferred. However, liposomes can also be used to deliver the antibody, or an antibody fragment, into cells. Where antibody fragments are used, the smallest inhibitory fragment that specifically binds to the binding domain of the target protein is preferred. For example, based upon the variable-region sequences of an antibody, peptide molecules can be designed that retain the ability to bind the target protein sequence. Such peptides can be synthesized chemically and/or produced by recombinant DNA technology. See,

e.g., Marasco et al., 1993 Proc. Natl. Acad. Sci. USA, 90: 7889-7893. The formulation herein can also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Alternatively, or in addition, the composition can comprise an agent that enhances its function, such as, for example, a cytotoxic agent, cytokine, chemotherapeutic agent, or growth-inhibitory agent. Such molecules are suitably present in combination in amounts that are effective for the purpose intended. The active ingredients can also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles, and nanocapsules) or in macroemulsions.

The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

Sustained-release preparations can be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, *e.g.*, films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and? ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT TM (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods.

The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

### **Screening and Detection Methods**

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The isolated nucleic acid molecules of the invention can be used to express ORX protein (e.g., via a recombinant expression vector in a host cell in gene therapy applications), to detect ORX mRNA (e.g., in a biological sample) or a genetic lesion in an ORX gene, and to modulate

ORX activity, as described further, below. In addition, the ORX proteins can be used to screen drugs or compounds that modulate the ORX protein activity or expression as well as to treat disorders characterized by insufficient or excessive production of ORX protein or production of ORX protein forms that have decreased or aberrant activity compared to ORX wild-type protein. In addition, the anti-ORX antibodies of the invention can be used to detect and isolate ORX proteins and modulate ORX activity. For example, ORX activity includes growth and differentiation, antibody production, and tumor growth.

The invention further pertains to novel agents identified by the screening assays described herein and uses thereof for treatments as described, *supra*.

Screening Assays

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The invention provides a method (also referred to herein as a "screening assay") for identifying modulators, *i.e.*, candidate or test compounds or agents (*e.g.*, peptides, peptidomimetics, small molecules or other drugs) that bind to ORX proteins or have a stimulatory or inhibitory effect on, *e.g.*, ORX protein expression or ORX protein activity. The invention also includes compounds identified in the screening assays described herein.

In one embodiment, the invention provides assays for screening candidate or test compounds which bind to or modulate the activity of the membrane-bound form of an ORX protein or polypeptide or biologically-active portion thereof. The test compounds of the invention can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the "one-bead one-compound" library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds. See, e.g., Lam, 1997. Anticancer Drug Design 12: 145.

A "small molecule" as used herein, is meant to refer to a composition that has a molecular weight of less than about 5 kD and most preferably less than about 4 kD. Small molecules can be, e.g., nucleic acids, peptides, polypeptides, peptidomimetics, carbohydrates, lipids or other organic or inorganic molecules. Libraries of chemical and/or biological mixtures, such as fungal, bacterial, or algal extracts, are known in the art and can be screened with any of the assays of the invention.

Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt, et al., 1993. Proc. Natl. Acad. Sci. U.S.A. 90: 6909; Erb, et al., 1994. Proc. Natl. Acad. Sci. U.S.A. 91: 11422; Zuckermann, et al., 1994. J. Med. Chem. 37: 2678; Cho, et al., 1993. Science 261: 1303; Carrell, et al., 1994. Angew. Chem. Int. Ed. Engl. 33: 2059; Carell, et al., 1994. Angew. Chem. Int. Ed. Engl. 33: 2061; and Gallop, et al., 1994. J. Med. Chem. 37: 1233.

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Libraries of compounds may be presented in solution (e.g., Houghten, 1992. Biotechniques 13: 412-421), or on beads (Lam, 1991. Nature 354: 82-84), on chips (Fodor, 1993. Nature 364: 555-556), bacteria (Ladner, U.S. Patent No. 5,223,409), spores (Ladner, U.S. Patent 5,233,409), plasmids (Cull, et al., 1992. Proc. Natl. Acad. Sci. USA 89: 1865-1869) or on phage (Scott and Smith, 1990. Science 249: 386-390; Devlin, 1990. Science 249: 404-406; Cwirla, et al., 1990. Proc. Natl. Acad. Sci. U.S.A. 87: 6378-6382; Felici, 1991. J. Mol. Biol. 222: 301-310; Ladner, U.S. Patent No. 5,233,409.).

In one embodiment, an assay is a cell-based assay in which a cell which expresses a membrane-bound form of ORX protein, or a biologically-active portion thereof, on the cell surface is contacted with a test compound and the ability of the test compound to bind to an ORX protein determined. The cell, for example, can be of mammalian origin or a yeast cell. Determining the ability of the test compound to bind to the ORX protein can be accomplished, for example, by coupling the test compound with a radioisotope or enzymatic label such that binding of the test compound to the ORX protein or biologically-active portion thereof can be determined by detecting the labeled compound in a complex. For example, test compounds can be labeled with <sup>125</sup>I, <sup>35</sup>S, <sup>14</sup>C, or <sup>3</sup>H, either directly or indirectly, and the radioisotope detected by direct counting of radioemission or by scintillation counting. Alternatively, test compounds can be enzymatically-labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product. In one embodiment, the assay comprises contacting a cell which expresses a membrane-bound form of ORX protein, or a biologically-active portion thereof, on the cell surface with a known compound which binds ORX to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with an ORX protein, wherein determining the ability of the test compound to interact with an

ORX protein comprises determining the ability of the test compound to preferentially bind to ORX protein or a biologically-active portion thereof as compared to the known compound.

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In another embodiment, an assay is a cell-based assay comprising contacting a cell expressing a membrane-bound form of ORX protein, or a biologically-active portion thereof, on the cell surface with a test compound and determining the ability of the test compound to modulate (e.g., stimulate or inhibit) the activity of the ORX protein or biologically-active portion thereof. Determining the ability of the test compound to modulate the activity of ORX or a biologically-active portion thereof can be accomplished, for example, by determining the ability of the ORX protein to bind to or interact with an ORX target molecule. As used herein, a "target molecule" is a molecule with which an ORX protein binds or interacts in nature, for example, a molecule on the surface of a cell which expresses an ORX interacting protein, a molecule on the surface of a second cell, a molecule in the extracellular milieu, a molecule associated with the internal surface of a cell membrane or a cytoplasmic molecule. An ORX target molecule can be a non-ORX molecule or an ORX protein or polypeptide of the invention In one embodiment, an ORX target molecule is a component of a signal transduction pathway that facilitates transduction of an extracellular signal (e.g. a signal generated by binding of a compound to a membrane-bound ORX molecule) through the cell membrane and into the cell. The target, for example, can be a second intercellular protein that has catalytic activity or a protein that facilitates the association of downstream signaling molecules with ORX.

Determining the ability of the ORX protein to bind to or interact with an ORX target molecule can be accomplished by one of the methods described above for determining direct binding. In one embodiment, determining the ability of the ORX protein to bind to or interact with an ORX target molecule can be accomplished by determining the activity of the target molecule. For example, the activity of the target molecule can be determined by detecting induction of a cellular second messenger of the target (*i.e.* intracellular Ca<sup>2+</sup>, diacylglycerol, IP<sub>3</sub>, etc.), detecting catalytic/enzymatic activity of the target an appropriate substrate, detecting the induction of a reporter gene (comprising an ORX-responsive regulatory element operatively linked to a nucleic acid encoding a detectable marker, *e.g.*, luciferase), or detecting a cellular response, for example, cell survival, cellular differentiation, or cell proliferation.

In yet another embodiment, an assay of the invention is a cell-free assay comprising contacting an ORX protein or biologically-active portion thereof with a test compound and

determining the ability of the test compound to bind to the ORX protein or biologically-active portion thereof. Binding of the test compound to the ORX protein can be determined either directly or indirectly as described above. In one such embodiment, the assay comprises contacting the ORX protein or biologically-active portion thereof with a known compound which binds ORX to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with an ORX protein, wherein determining the ability of the test compound to interact with an ORX protein comprises determining the ability of the test compound to preferentially bind to ORX or biologically-active portion thereof as compared to the known compound.

In still another embodiment, an assay is a cell-free assay comprising contacting ORX protein or biologically-active portion thereof with a test compound and determining the ability of the test compound to modulate (e.g. stimulate or inhibit) the activity of the ORX protein or biologically-active portion thereof. Determining the ability of the test compound to modulate the activity of ORX can be accomplished, for example, by determining the ability of the ORX protein to bind to an ORX target molecule by one of the methods described above for determining direct binding. In an alternative embodiment, determining the ability of the test compound to modulate the activity of ORX protein can be accomplished by determining the ability of the ORX protein further modulate an ORX target molecule. For example, the catalytic/enzymatic activity of the target molecule on an appropriate substrate can be determined as described above.

In yet another embodiment, the cell-free assay comprises contacting the ORX protein or biologically-active portion thereof with a known compound which binds ORX protein to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with an ORX protein, wherein determining the ability of the test compound to interact with an ORX protein comprises determining the ability of the ORX protein to preferentially bind to or modulate the activity of an ORX target molecule.

The cell-free assays of the invention are amenable to use of both the soluble form or the membrane-bound form of ORX protein. In the case of cell-free assays comprising the membrane-bound form of ORX protein, it may be desirable to utilize a solubilizing agent such that the membrane-bound form of ORX protein is maintained in solution. Examples of such solubilizing agents include non-ionic detergents such as n-octylglucoside, n-dodecylglucoside,

n-dodecylmaltoside, octanoyl-N-methylglucamide, decanoyl-N-methylglucamide, Triton® X-100, Triton® X-114, Thesit®, Isotridecypoly(ethylene glycol ether)<sub>n</sub>, N-dodecyl--N,N-dimethyl-3-ammonio-1-propane sulfonate, 3-(3-cholamidopropyl) dimethylamminiol-1-propane sulfonate (CHAPS), or 3-(3-cholamidopropyl)dimethylamminiol-2-hydroxy-1-propane sulfonate (CHAPSO).

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In more than one embodiment of the above assay methods of the invention, it may be desirable to immobilize either ORX protein or its target molecule to facilitate separation of complexed from uncomplexed forms of one or both of the proteins, as well as to accommodate automation of the assay. Binding of a test compound to ORX protein, or interaction of ORX protein with a target molecule in the presence and absence of a candidate compound, can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtiter plates, test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein can be provided that adds a domain that allows one or both of the proteins to be bound to a matrix. For example, GST-ORX fusion proteins or GST-target fusion proteins can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtiter plates, that are then combined with the test compound or the test compound and either the non-adsorbed target protein or ORX protein, and the mixture is incubated under conditions conducive to complex formation (e.g., at physiological conditions for salt and pH). Following incubation, the beads or microtiter plate wells are washed to remove any unbound components, the matrix immobilized in the case of beads, complex determined either directly or indirectly, for example, as described, supra. Alternatively, the complexes can be dissociated from the matrix, and the level of ORX protein binding or activity determined using standard techniques.

Other techniques for immobilizing proteins on matrices can also be used in the screening assays of the invention. For example, either the ORX protein or its target molecule can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated ORX protein or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques well-known within the art (e.g., biotinylation kit, Pierce Chemicals, Rockford, Ill.), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). Alternatively, antibodies reactive with ORX protein or target molecules, but which do not interfere with binding of the ORX protein to its target molecule, can be derivatized to the wells of the plate, and unbound target or ORX protein trapped in the wells by antibody conjugation. Methods for detecting such

complexes, in addition to those described above for the GST-immobilized complexes, include immunodetection of complexes using antibodies reactive with the ORX protein or target molecule, as well as enzyme-linked assays that rely on detecting an enzymatic activity associated with the ORX protein or target molecule.

In another embodiment, modulators of ORX protein expression are identified in a method wherein a cell is contacted with a candidate compound and the expression of ORX mRNA or protein in the cell is determined. The level of expression of ORX mRNA or protein in the presence of the candidate compound is compared to the level of expression of ORX mRNA or protein in the absence of the candidate compound. The candidate compound can then be identified as a modulator of ORX mRNA or protein expression based upon this comparison. For example, when expression of ORX mRNA or protein is greater (*i.e.*, statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of ORX mRNA or protein expression. Alternatively, when expression of ORX mRNA or protein is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of ORX mRNA or protein expression. The level of ORX mRNA or protein expression in the cells can be determined by methods described herein for detecting ORX mRNA or protein.

In yet another aspect of the invention, the ORX proteins can be used as "bait proteins" in a two-hybrid assay or three hybrid assay (*see, e.g.*, U.S. Patent No. 5,283,317; Zervos, *et al.*, 1993. *Cell* 72: 223-232; Madura, *et al.*, 1993. *J. Biol. Chem.* 268: 12046-12054; Bartel, *et al.*, 1993. *Biotechniques* 14: 920-924; Iwabuchi, *et al.*, 1993. *Oncogene* 8: 1693-1696; and Brent WO 94/10300), to identify other proteins that bind to or interact with ORX ("ORX-binding proteins" or "ORX-bp") and modulate ORX activity. Such ORX-binding proteins are also likely to be involved in the propagation of signals by the ORX proteins as, for example, upstream or downstream elements of the ORX pathway.

The two-hybrid system is based on the modular nature of most transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the assay utilizes two different DNA constructs. In one construct, the gene that codes for ORX is fused to a gene encoding the DNA binding domain of a known transcription factor (e.g., GAL-4). In the other construct, a DNA sequence, from a library of DNA sequences, that encodes an unidentified protein ("prey" or "sample") is fused to a gene that codes for the activation domain of the known

transcription factor. If the "bait" and the "prey" proteins are able to interact, *in vivo*, forming an ORX-dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (*e.g.*, LacZ) that is operably linked to a transcriptional regulatory site responsive to the transcription factor. Expression of the reporter gene can be detected and cell colonies containing the functional transcription factor can be isolated and used to obtain the cloned gene that encodes the protein which interacts with ORX.

The invention further pertains to novel agents identified by the aforementioned screening assays and uses thereof for treatments as described herein.

# **Detection Assays**

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Portions or fragments of the cDNA sequences identified herein (and the corresponding complete gene sequences) can be used in numerous ways as polynucleotide reagents. By way of example, and not of limitation, these sequences can be used to: (i) identify an individual from a minute biological sample (tissue typing); and (ii) aid in forensic identification of a biological sample. Some of these applications are described in the subsections, below.

Tissue Typing

The ORX sequences of the invention can be used to identify individuals from minute biological samples. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identification. The sequences of the invention are useful as additional DNA markers for RFLP ("restriction fragment length polymorphisms," described in U.S. Patent No. 5,272,057).

Furthermore, the sequences of the invention can be used to provide an alternative technique that determines the actual base-by-base DNA sequence of selected portions of an individual's genome. Thus, the ORX sequences described herein can be used to prepare two PCR primers from the 5'- and 3'-termini of the sequences. These primers can then be used to amplify an individual's DNA and subsequently sequence it.

Panels of corresponding DNA sequences from individuals, prepared in this manner, can provide unique individual identifications, as each individual will have a unique set of such DNA sequences due to allelic differences. The sequences of the invention can be used to obtain such identification sequences from individuals and from tissue. The ORX sequences of the invention

uniquely represent portions of the human genome. Allelic variation occurs to some degree in the coding regions of these sequences, and to a greater degree in the noncoding regions. It is estimated that allelic variation between individual humans occurs with a frequency of about once per each 500 bases. Much of the allelic variation is due to single nucleotide polymorphisms (SNPs), which include restriction fragment length polymorphisms (RFLPs).

Each of the sequences described herein can, to some degree, be used as a standard against which DNA from an individual can be compared for identification purposes. Because greater numbers of polymorphisms occur in the noncoding regions, fewer sequences are necessary to differentiate individuals. The noncoding sequences can comfortably provide positive individual identification with a panel of perhaps 10 to 1,000 primers that each yield a noncoding amplified sequence of 100 bases. If predicted coding sequences are used, a more appropriate number of primers for positive individual identification would be 500-2,000.

#### **Predictive Medicine**

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The invention also pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, pharmacogenomics, and monitoring clinical trials are used for prognostic (predictive) purposes to thereby treat an individual prophylactically. Accordingly, one aspect of the invention relates to diagnostic assays for determining ORX protein and/or nucleic acid expression as well as ORX activity, in the context of a biological sample (e.g., blood, serum, cells, tissue) to thereby determine whether an individual is afflicted with a disease or disorder, or is at risk of developing a disorder, associated with aberrant ORX expression or activity. Disorders associated with aberrant ORX expression of activity include, for example, neurodegenerative, cell proliferative, angiogenic, hematopoietic, immunological, inflammatory, and tumor-related disorders and/or pathologies.

The invention also provides for prognostic (or predictive) assays for determining whether an individual is at risk of developing a disorder associated with ORX protein, nucleic acid expression or activity. For example, mutations in an ORX gene can be assayed in a biological sample. Such assays can be used for prognostic or predictive purpose to thereby prophylactically treat an individual prior to the onset of a disorder characterized by or associated with ORX protein, nucleic acid expression, or biological activity.

Another aspect of the invention provides methods for determining ORX protein, nucleic acid expression or activity in an individual to thereby select appropriate therapeutic or prophylactic agents for that individual (referred to herein as "pharmacogenomics"). Pharmacogenomics allows for the selection of agents (e.g., drugs) for therapeutic or prophylactic treatment of an individual based on the genotype of the individual (e.g., the genotype of the individual examined to determine the ability of the individual to respond to a particular agent.)

Yet another aspect of the invention pertains to monitoring the influence of agents (e.g., drugs, compounds) on the expression or activity of ORX in clinical trials.

These and other agents are described in further detail in the following sections.

Diagnostic Assays

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An exemplary method for detecting the presence or absence of ORX in a biological sample involves obtaining a biological sample from a test subject and contacting the biological sample with a compound or an agent capable of detecting ORX protein or nucleic acid (e.g., mRNA, genomic DNA) that encodes ORX protein such that the presence of ORX is detected in the biological sample. An agent for detecting ORX mRNA or genomic DNA is a labeled nucleic acid probe capable of hybridizing to ORX mRNA or genomic DNA. The nucleic acid probe can be, for example, a full-length ORX nucleic acid, or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to ORX mRNA or genomic DNA. Other suitable probes for use in the diagnostic assays of the invention are described herein.

One agent for detecting ORX protein is an antibody capable of binding to ORX protein, preferably an antibody with a detectable label. Antibodies directed against a protein of the invention may be used in methods known within the art relating to the localization and/or quantitation of the protein (e.g., for use in measuring levels of the protein within appropriate physiological samples, for use in diagnostic methods, for use in imaging the protein, and the like). In a given embodiment, antibodies against the proteins, or derivatives, fragments, analogs or homologs thereof, that contain the antigen binding domain, are utilized as pharmacologically-active compounds.

An antibody specific for a protein of the invention can be used to isolate the protein by standard techniques, such as immunoaffinity chromatography or immunoprecipitation. Such an antibody can facilitate the purification of the natural protein antigen from cells and of

recombinantly produced antigen expressed in host cells. Moreover, such an antibody can be used to detect the antigenic protein (e.g., in a cellular lysate or cell supernatant) in order to evaluate the abundance and pattern of expression of the antigenic protein. Antibodies directed against the protein can be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, e.g., to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling (i.e., physically linking) the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase,  $\beta$ -galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include  $^{125}$ I,  $^{131}$ I,  $^{35}$ S or  $^{3}$ H.

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Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (e.g., Fab or F(ab')<sub>2</sub>) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (i.e., physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently-labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently-labeled streptavidin. The term "biological sample" is intended to include tissues, cells and biological fluids isolated from a subject, as well as tissues, cells and fluids present within a subject. That is, the detection method of the invention can be used to detect ORX mRNA, protein, or genomic DNA in a biological sample in vitro as well as in vivo. For example, in vitro techniques for detection of ORX mRNA include Northern hybridizations and in situ hybridizations. In vitro techniques for detection of ORX protein include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations, and immunofluorescence. In vitro techniques for detection of ORX genomic DNA include Southern hybridizations. Furthermore, in vivo techniques for detection of ORX protein include

introducing into a subject a labeled anti-ORX antibody. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

In one embodiment, the biological sample contains protein molecules from the test subject. Alternatively, the biological sample can contain mRNA molecules from the test subject or genomic DNA molecules from the test subject. A preferred biological sample is a peripheral blood leukocyte sample isolated by conventional means from a subject.

In one embodiment, the methods further involve obtaining a control biological sample from a control subject, contacting the control sample with a compound or agent capable of detecting ORX protein, mRNA, or genomic DNA, such that the presence of ORX protein, mRNA or genomic DNA is detected in the biological sample, and comparing the presence of ORX protein, mRNA or genomic DNA in the control sample with the presence of ORX protein, mRNA or genomic DNA in the test sample.

The invention also encompasses kits for detecting the presence of ORX in a biological sample. For example, the kit can comprise: a labeled compound or agent capable of detecting ORX protein or mRNA in a biological sample; means for determining the amount of ORX in the sample; and means for comparing the amount of ORX in the sample with a standard. The compound or agent can be packaged in a suitable container. The kit can further comprise instructions for using the kit to detect ORX protein or nucleic acid.

Prognostic Assays

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The diagnostic methods described herein can furthermore be utilized to identify subjects having or at risk of developing a disease or disorder associated with aberrant ORX expression or activity. For example, the assays described herein, such as the preceding diagnostic assays or the following assays, can be utilized to identify a subject having or at risk of developing a disorder associated with ORX protein, nucleic acid expression or activity. Such disorders include for example, neurodegenerative, cell proliferative, angiogenic, hematopoietic, immunological, inflammatory, and tumor-related disorders and/or pathologies.

Alternatively, the prognostic assays can be utilized to identify a subject having or at risk for developing a disease or disorder. Thus, the invention provides a method for identifying a disease or disorder associated with aberrant ORX expression or activity in which a test sample is obtained from a subject and ORX protein or nucleic acid (e.g., mRNA, genomic DNA) is

detected, wherein the presence of ORX protein or nucleic acid is diagnostic for a subject having or at risk of developing a disease or disorder associated with aberrant ORX expression or activity. As used herein, a "test sample" refers to a biological sample obtained from a subject of interest. For example, a test sample can be a biological fluid (e.g., serum), cell sample, or tissue.

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Furthermore, the prognostic assays described herein can be used to determine whether a subject can be administered an agent (e.g., an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate) to treat a disease or disorder associated with aberrant ORX expression or activity. For example, such methods can be used to determine whether a subject can be effectively treated with an agent for a disorder. Thus, the invention provides methods for determining whether a subject can be effectively treated with an agent for a disorder associated with aberrant ORX expression or activity in which a test sample is obtained and ORX protein or nucleic acid is detected (e.g., wherein the presence of ORX protein or nucleic acid is diagnostic for a subject that can be administered the agent to treat a disorder associated with aberrant ORX expression or activity).

The methods of the invention can also be used to detect genetic lesions in an ORX gene, thereby determining if a subject with the lesioned gene is at risk for a disorder characterized by aberrant cell proliferation and/or differentiation. In various embodiments, the methods include detecting, in a sample of cells from the subject, the presence or absence of a genetic lesion characterized by at least one of an alteration affecting the integrity of a gene encoding an ORX-protein, or the misexpression of the ORX gene. For example, such genetic lesions can be detected by ascertaining the existence of at least one of: (i) a deletion of one or more nucleotides from an ORX gene; (ii) an addition of one or more nucleotides to an ORX gene; (iii) a substitution of one or more nucleotides of an ORX gene, (iv) a chromosomal rearrangement of an ORX gene; (v) an alteration in the level of a messenger RNA transcript of an ORX gene, (vi) aberrant modification of an ORX gene, such as of the methylation pattern of the genomic DNA, (vii) the presence of a non-wild-type splicing pattern of a messenger RNA transcript of an ORX gene, (viii) a non-wild-type level of an ORX protein, (ix) allelic loss of an ORX gene, and (x) inappropriate post-translational modification of an ORX protein. As described herein, there are a large number of assay techniques known in the art which can be used for detecting lesions in an ORX gene. A preferred biological sample is a peripheral blood leukocyte sample isolated by

conventional means from a subject. However, any biological sample containing nucleated cells may be used, including, for example, buccal mucosal cells.

In certain embodiments, detection of the lesion involves the use of a probe/primer in a polymerase chain reaction (PCR) (*see, e.g.*, U.S. Patent Nos. 4,683,195 and 4,683,202), such as anchor PCR or RACE PCR, or, alternatively, in a ligation chain reaction (LCR) (*see, e.g.*, Landegran, *et al.*, 1988. *Science* 241: 1077-1080; and Nakazawa, *et al.*, 1994. *Proc. Natl. Acad. Sci. USA* 91: 360-364), the latter of which can be particularly useful for detecting point mutations in the ORX-gene (*see*, Abravaya, *et al.*, 1995. *Nucl. Acids Res.* 23: 675-682). This method can include the steps of collecting a sample of cells from a patient, isolating nucleic acid (*e.g.*, genomic, mRNA or both) from the cells of the sample, contacting the nucleic acid sample with one or more primers that specifically hybridize to an ORX gene under conditions such that hybridization and amplification of the ORX gene (if present) occurs, and detecting the presence or absence of an amplification product, or detecting the size of the amplification product and comparing the length to a control sample. It is anticipated that PCR and/or LCR may be desirable to use as a preliminary amplification step in conjunction with any of the techniques used for detecting mutations described herein.

Alternative amplification methods include: self sustained sequence replication (see, Guatelli, et al., 1990. Proc. Natl. Acad. Sci. USA 87: 1874-1878), transcriptional amplification system (see, Kwoh, et al., 1989. Proc. Natl. Acad. Sci. USA 86: 1173-1177); Qβ Replicase (see, Lizardi, et al, 1988. BioTechnology 6: 1197), or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers.

In an alternative embodiment, mutations in an ORX gene from a sample cell can be identified by alterations in restriction enzyme cleavage patterns. For example, sample and control DNA is isolated, amplified (optionally), digested with one or more restriction endonucleases, and fragment length sizes are determined by gel electrophoresis and compared. Differences in fragment length sizes between sample and control DNA indicates mutations in the sample DNA. Moreover, the use of sequence specific ribozymes (*see, e.g.*, U.S. Patent No. 5,493,531) can be used to score for the presence of specific mutations by development or loss of a ribozyme cleavage site.

In other embodiments, genetic mutations in ORX can be identified by hybridizing a sample and control nucleic acids, e.g., DNA or RNA, to high-density arrays containing hundreds or thousands of oligonucleotides probes. See, e.g., Cronin, et al., 1996. Human Mutation 7: 244-255; Kozal, et al., 1996. Nat. Med. 2: 753-759. For example, genetic mutations in ORX can be identified in two dimensional arrays containing light-generated DNA probes as described in Cronin, et al., supra. Briefly, a first hybridization array of probes can be used to scan through long stretches of DNA in a sample and control to identify base changes between the sequences by making linear arrays of sequential overlapping probes. This step allows the identification of point mutations. This is followed by a second hybridization array that allows the characterization of specific mutations by using smaller, specialized probe arrays complementary to all variants or mutations detected. Each mutation array is composed of parallel probe sets, one complementary to the wild-type gene and the other complementary to the mutant gene.

In yet another embodiment, any of a variety of sequencing reactions known in the art can be used to directly sequence the ORX gene and detect mutations by comparing the sequence of the sample ORX with the corresponding wild-type (control) sequence. Examples of sequencing reactions include those based on techniques developed by Maxim and Gilbert, 1977. *Proc. Natl. Acad. Sci. USA* 74: 560 or Sanger, 1977. *Proc. Natl. Acad. Sci. USA* 74: 5463. It is also contemplated that any of a variety of automated sequencing procedures can be utilized when performing the diagnostic assays (*see, e.g.*, Naeve, *et al.*, 1995. *Biotechniques* 19: 448), including sequencing by mass spectrometry (see, *e.g.*, PCT International Publication No. WO 94/16101; Cohen, *et al.*, 1996. *Adv. Chromatography* 36: 127-162; and Griffin, *et al.*, 1993. *Appl. Biochem. Biotechnol.* 38: 147-159).

Other methods for detecting mutations in the ORX gene include methods in which protection from cleavage agents is used to detect mismatched bases in RNA/RNA or RNA/DNA heteroduplexes. See, e.g., Myers, et al., 1985. Science 230: 1242. In general, the art technique of "mismatch cleavage" starts by providing heteroduplexes of formed by hybridizing (labeled) RNA or DNA containing the wild-type ORX sequence with potentially mutant RNA or DNA obtained from a tissue sample. The double-stranded duplexes are treated with an agent that cleaves single-stranded regions of the duplex such as which will exist due to basepair mismatches between the control and sample strands. For instance, RNA/DNA duplexes can be treated with RNase and DNA/DNA hybrids treated with S<sub>1</sub> nuclease to enzymatically digesting the

mismatched regions. In other embodiments, either DNA/DNA or RNA/DNA duplexes can be treated with hydroxylamine or osmium tetroxide and with piperidine in order to digest mismatched regions. After digestion of the mismatched regions, the resulting material is then separated by size on denaturing polyacrylamide gels to determine the site of mutation. See, e.g., Cotton, et al., 1988. Proc. Natl. Acad. Sci. USA 85: 4397; Saleeba, et al., 1992. Methods Enzymol. 217: 286-295. In an embodiment, the control DNA or RNA can be labeled for detection.

In still another embodiment, the mismatch cleavage reaction employs one or more proteins that recognize mismatched base pairs in double-stranded DNA (so called "DNA mismatch repair" enzymes) in defined systems for detecting and mapping point mutations in ORX cDNAs obtained from samples of cells. For example, the mutY enzyme of *E. coli* cleaves A at G/A mismatches and the thymidine DNA glycosylase from HeLa cells cleaves T at G/T mismatches. *See, e.g.,* Hsu, *et al.,* 1994. *Carcinogenesis* 15: 1657-1662. According to an exemplary embodiment, a probe based on an ORX sequence, *e.g.,* a wild-type ORX sequence, is hybridized to a cDNA or other DNA product from a test cell(s). The duplex is treated with a DNA mismatch repair enzyme, and the cleavage products, if any, can be detected from electrophoresis protocols or the like. *See, e.g.,* U.S. Patent No. 5,459,039.

In other embodiments, alterations in electrophoretic mobility will be used to identify mutations in ORX genes. For example, single strand conformation polymorphism (SSCP) may be used to detect differences in electrophoretic mobility between mutant and wild type nucleic acids. See, e.g., Orita, et al., 1989. Proc. Natl. Acad. Sci. USA: 86: 2766; Cotton, 1993. Mutat. Res. 285: 125-144; Hayashi, 1992. Genet. Anal. Tech. Appl. 9: 73-79. Single-stranded DNA fragments of sample and control ORX nucleic acids will be denatured and allowed to renature. The secondary structure of single-stranded nucleic acids varies according to sequence, the resulting alteration in electrophoretic mobility enables the detection of even a single base change. The DNA fragments may be labeled or detected with labeled probes. The sensitivity of the assay may be enhanced by using RNA (rather than DNA), in which the secondary structure is more sensitive to a change in sequence. In one embodiment, the subject method utilizes heteroduplex analysis to separate double stranded heteroduplex molecules on the basis of changes in electrophoretic mobility. See, e.g., Keen, et al., 1991. Trends Genet. 7: 5.

In yet another embodiment, the movement of mutant or wild-type fragments in polyacrylamide gels containing a gradient of denaturant is assayed using denaturing gradient gel electrophoresis (DGGE). See, e.g., Myers, et al., 1985. Nature 313: 495. When DGGE is used as the method of analysis, DNA will be modified to insure that it does not completely denature, for example by adding a GC clamp of approximately 40 bp of high-melting GC-rich DNA by PCR. In a further embodiment, a temperature gradient is used in place of a denaturing gradient to identify differences in the mobility of control and sample DNA. See, e.g., Rosenbaum and Reissner, 1987. Biophys. Chem. 265: 12753.

Examples of other techniques for detecting point mutations include, but are not limited to, selective oligonucleotide hybridization, selective amplification, or selective primer extension. For example, oligonucleotide primers may be prepared in which the known mutation is placed centrally and then hybridized to target DNA under conditions that permit hybridization only if a perfect match is found. See, e.g., Saiki, et al., 1986. Nature 324: 163; Saiki, et al., 1989. Proc. Natl. Acad. Sci. USA 86: 6230. Such allele specific oligonucleotides are hybridized to PCR amplified target DNA or a number of different mutations when the oligonucleotides are attached to the hybridizing membrane and hybridized with labeled target DNA.

Alternatively, allele specific amplification technology that depends on selective PCR amplification may be used in conjunction with the instant invention. Oligonucleotides used as primers for specific amplification may carry the mutation of interest in the center of the molecule (so that amplification depends on differential hybridization; see, e.g., Gibbs, et al., 1989. Nucl. Acids Res. 17: 2437-2448) or at the extreme 3'-terminus of one primer where, under appropriate conditions, mismatch can prevent, or reduce polymerase extension (see, e.g., Prossner, 1993. Tibtech. 11: 238). In addition it may be desirable to introduce a novel restriction site in the region of the mutation to create cleavage-based detection. See, e.g., Gasparini, et al., 1992. Mol. Cell Probes 6: 1. It is anticipated that in certain embodiments amplification may also be performed using Taq ligase for amplification. See, e.g., Barany, 1991. Proc. Natl. Acad. Sci. USA 88: 189. In such cases, ligation will occur only if there is a perfect match at the 3'-terminus of the 5' sequence, making it possible to detect the presence of a known mutation at a specific site by looking for the presence or absence of amplification.

The methods described herein may be performed, for example, by utilizing pre-packaged diagnostic kits comprising at least one probe nucleic acid or antibody reagent described herein,

which may be conveniently used, e.g., in clinical settings to diagnose patients exhibiting symptoms or family history of a disease or illness involving an ORX gene.

Furthermore, any cell type or tissue, preferably peripheral blood leukocytes, in which ORX is expressed may be utilized in the prognostic assays described herein. However, any biological sample containing nucleated cells may be used, including, for example, buccal mucosal cells.

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The invention will be further described in the following examples, which do not limit the scope of the invention described in the claims.

## **EXAMPLE 1:** Cloning and analysis of ORX-like sequences in primates and mouse.

The isolation of ORX-related sequences has been described in Rouquier et al., Nature Genet. (1998) 18, 243-50 and Rouquier et al. (1998) Hum. Mol. Genet. 7, 1337-1345. Briefly, 15 100 ng of genomic DNA from each species was subjected to PCR using consensus ORX primers OR5B-OR3B (OR5B (TM2), 5'-CCCATGTA(T/C)TT(G/C/T)TT(C/T)CTC(A/G/T)(G/C)(C/T)AA(C/T)(T/C)T(G/A)TC-3'; PMY(F/L)FL(S/A/T/G/C)NLS; OR3B (TM7), (SEQ ID NO: 432) 5'-AG(A/G)C(A/T)(A/G)TAIATGAAIGG(A/G)TTCAICAT-3' (SEQ ID NO:433); 20 M(L/F/V/I)NPF(I/M)Y(S/C)L) (SEQ ID NO:434). See Ben-Arie et al., (1994) Hum. Molec. Genet. 3, 229-35. A second pair of consensus primers, OR3.1-OR7.1 (OR3.1 (TM3), 5'-GCIATGGCITA(C/T)GA(C/T)(A/C)GITA-3' (SEQ ID NO:435); AMAYD(S/R)Y (SEQ ID NO:436); OR7.1 (TM7), 5'-A(A/G)I(G/C)(A/T)(A/G)TA(A/G/T)AT(A/G)AAIGG(A/G)TT-3' (SEQ ID NO:437); NPFIY(S/R/T/C/W)(L/F)(SEQ ID NO:438), was also used to amplify primate 25 ORX sequences. See Freitag et al. (1998) J. Comp. Physiol. 183, 635-50 and Freitag et al., (1999) Gene 226, 165-74.

PCR products were subcloned in the TA vector (InVitrogen), and recombinant clones were identified by PCR. Sequencing of the ORX sequences was performed and sequences were assembled and analyzed. The following species were studied: human (Homo sapiens, HSA), chimpanzee (Pan troglodytes, PTR), gorilla (Gorilla gorilla, GGO), orangutan (Pongo pygmaeus, PPY), gibbon (Hylobates lar, HLA), macaque (Macaca sylvanus, MSY), baboon (Papio papio,

PPA), marmoset (Callithrix jacchus, CJA), squirrel-monkey (Saimiri sciureus, SSC, and Saimiri boliviensis, SBO), lemur (Eulemur fulvus, EFU, and Eulemur rubriventer, ERU), and mouse (Mus musculus domesticus, MMU). In addition, a few zebrafish (Danio rerio, DRE) sequences were also characterized using primers OR3.1-OR7.1.

Pairwise sequence comparisons and multiple alignments were performed using Gap and PileUp from the GCG package (Wisconsin Package version 8).

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### **EXAMPLE 2:** Construction and screening of an ORX-specific mouse sublibrary.

Mouse ORX clones obtained by PCR as described above were gridded in 96-well microtiter dishes (1536 clones in 8 plates). For hybridization screening, the clones were robot-spotted in duplicate on high-density filters as described in Rouquier et al. (1999) *Mamm. Genome* 10, 1172-75.. Approximately 90% of the clones were identified as ORX genes. This library was screened to identify clones hybridizing to human ORX pseudogene sequences. Human plasmid DNA probes were radiolabeled to a specific activity of 108-109 cpm/μg by random hexamer priming using (□-32P)-dCTP (Amersham) as described in Feinberg et al. (1983) *Anal. Biochem.* 132, 6-13. Filter hybridizations were carried out under standard hybridization conditions, and exposed to Kodak X-ray film at -80°C. *See* Rouquier et al., (1993) *Genomics* 17, 330-40.

Three human ORX probes were used: OR1-72, OR912-47, OR15-71 (DDBJ/GenBank accession numbers U86218, U86230, U86296 respectively).

## **EXAMPLE 3:** Sequence analysis of mouse ORX sequences.

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To test whether mammals thought to be microsmatic or macrosmatic differ in the fraction of pseudogenes in their ORX repertoire, the ORX sequences in the mouse genome were surveyed. A mouse sublibrary enriched for ORX-related sequences amplified by PCR from the mouse genome was constructed, and nineteen randomly selected mouse ORX clones were sequenced. All 19 have an uninterrupted open-reading frame (ORF) and are potentially functional. These sequences group primarily in family 1 and vary from ~52 to >99% NSI. In addition, in an attempt to bias in favor of selecting mouse ORX pseudogenes, a search for mouse ORX sequences homologous to human pseudogenes was performed. One member was chosen from three different ORX pseudogene families: clones 1-72, 15-71 and 912-47 from chromosomes 1, 15 and 11, respectively. See Rouquier et al., (1998) Nature Genet. 18, 243-50. Each of these genes belongs to one of the 3 main groups of human ORX sequences and has accumulated a number of mutations such as stop codons and indel frameshifts. See id. The amino-acid sequence identity between these three ranges from 31% to 41%.

High density filters from the mouse ORX sublibrary were then hybridized separately with the three human pseudogene probes at a high stringency. Fourteen clones were sequenced on both strands. These sequences showed 38% to 53% ASI to the human sequences used to select them, indicating that they are not the orthologs of the human pseudogenes. All have an uninterrupted ORF from TM2 to TM7. Together, 33 mouse ORX sequences were sequenced, none of which contained characteristic features of pseudogenes.

#### OTHER EMBODIMENTS

While the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.